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(16)

No. 06-1249

Supreme Court, U.S.
FILED
MAY 27 2008
OFFICE OF THE CLERK

IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO
THE VERMONT SUPREME COURT

JOINT APPENDIX

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PETITION FOR CERTIORARI FILED MARCH 12, 2007
CERTIORARI GRANTED JANUARY 18, 2008

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SUPERIOR COURT
WASHINGTON SMALL CLAIMS COURT

Docket No. 670-12-01 Wncv

LEVINE vs. AMERICAN HOME PRODUCTS CORP.

Case Type:
Case Track: Not set
Case Status: Disposed
Court/Jury: Jury Trial
Next Hearing:

Last judge: Geoffrey W. Crawfor
Recused: Alan W. Cook

PARTIES

No.	Role	Litigant Name	Attorney Name	Telephone
p# 1	plf	Levine, Diana	Rubin, Richard I.	479-2514
p# 2	def	American Home Products Corp.	O'Rourke, R. Joseph	786-1000

DISPUTES

Dspt	Case	Name	Disputants	Dispo	Date
1	cmpl	Negligence	p#1 v p#2	jplfjt	03/12/04

MOTIONS/PETITIONS/REQUESTS FOR RELIEF

No.	Type	Status	Judge	Date
1	M/For Admission of Counsel (Grossi)	granted	MT	12/09/02

2	M/For Admission of Counsel (Petersen)	denied	GWC	08/02/04
3	M/For Admission of Counsel (Pariser)	denied	GWC	08/02/04
4	M/to Amend Complaint	granted	MT	04/03/03
5	M/for Summary Judgment	denied	AWC	12/23/03
6	M/in Limine (Phenergan Injection)	denied	AWC	02/20/04
7	M/in Limine (Black Box Warnings)	denied	AWC	02/20/04
8	M/in Limine (Dilution of Phenergan)	defer	AWC	02/20/04
9	M/in Limine (Corporate Intent)	granted	AWC	02/20/04
10	M/in Limine (Vistaril)	denied	AWC	02/20/04
11	M/in Limine to Exclude Unfairly Prej. Evid	defer	AWC	02/20/04
12	M/For Admission of Counsel			03/05/04
13	M/in Limine—Prior Claims			03/05/04
14	M/Emergency Request to Postpone Trial	moot	AWC	03/05/04
15	M/for Judgment as a Matter of Law			03/11/04
16	M/to Exclude Deposition Testimony	moot	GWC	03/09/04

17	M/for Judgment as a Matter of Law			03/11/04
18	M/(Assented) to Mo. for Enlargement of Tim	granted	GWC	03/31/04
19	M/for Judgment (Renewed) as a Matter of La	judge	GWC	05/20/04
20	M/for New Trial	judge	GWC	05/20/04

12/17/01 Diana Levine, Plaintiff.

(now Wyeth) American Home Products Corp. Defendant.

Negligence case filed by Plaintiff Diana Levine against Defendant (now Wyeth) American Home Products Corp. Jury trial requested.

Jury trial requested by Plaintiff Diana Levine.

Discovery: Discovery Certificate serving Plf's 1st Interrogs & Requests to produce filed by Atty Rubin.

letter advising of docket number assigned letter sent to Plaintiff Diana Levine.

* * *

01/22/02 Appearance entered by R. Joseph O'Rourke on behalf of Defendant (now Wyeth) American Home Products Corp.

Answer filed by Attorney R. Joseph O'Rourke for Defendant (now Wyeth)

American Home Products Corp.

Jury trial requested by Defendant (now Wyeth) American Home Products Corp.

Discovery: Discovery Certificate serving Deft's 1st Expert Interrogs & requests for production filed by Atty O'Rourke.

* * *

03/07/03 MPR 4) Motion to Amend Complaint filed by Plaintiff Diana Levine. Motion to Amend Complaint. Documents filed: Mo. to Amend Complaint; Memorandum; attachments.

* * *

04/03/03 Entry Order re MPR 4) Motion to Amend Complaint. M/Reaction Form. granted by MT. See Order.

Copies of Order mailed to counsel letter sent to Plaintiff Diana Levine and Defendant (now Wyeth) American Home Products Corp. and Co-counsel for Defendant Daniel S. Pariser and Co-counsel for Defendant Cara M. Petersen and Co-counsel for Defendant Peter T. Grossi, Jr.

* * *

05/15/03 MPR 5) Motion for Summary Judgment filed by Co-counsel for Defendant Peter T. Grossi, Jr. Motion for Summary Judgment. Documents filed: Mo. for Summary Judgment or; alternarively Partial Summary Judgment; Certificate of Service; Statement of Undisputed Material Facts; Memorandum of points in support; Exhibits.

* * *

07/18/03	Party 1 filed response to MPR 5.
08/05/03	Party 2 filed response to MPR 5.
	* * *
09/09/03	Party 1 filed response to MPR 5.
	* * *
11/10/03	Motion, Petition, Request held. AWC/CH.
	Entry Order by Judge Alan W. Cook: Mo. for Summary Judgment; under advisement.
	Case status changed.
	* * *
12/19/03	1 document filed by Attorney Richard I. Rubin for party 1: Amended Complaint.
12/23/03	Decision re: Wyeth's Mo. for Summary Judgment filed.
	MPR 5 status changed to denied.
	Copies of Order mailed to counsel letter sent to Plaintiff Diana Levine and Defendant (now Wyeth) American Home Products Corp. and Co-counsel for Defendant Daniel S. Pariser and Co-counsel for Defendant Cara M. Petersen and Co-counsel for Defendant Peter T. Grossi, Jr.
	Case status changed.
01/02/04	3 documents filed for party 5: Answer of Deft Wyeth to Plf's amended; complaint; Certificate of Service.
	* * *
03/08/04	Original Emergency request to Postpone trial filed by Atty O'Rourke.

Party 2 filed response to MPR 13.

Jury Trial held. GWC/CH.

03/09/04 MPR 16) Motion to Exclude Deposition Testimony filed by Plaintiff Diana Levine. Motion to Exclude Deposition Testimony. Documents filed: Mo. to Exclude Deposition Testimony; Exhibits.

MPR 16 status changed to moot.

Jury Trial held. GWC/CH.

03/10/04 Jury Trial held. GWC/CH.

03/11/04 MPR 15) Motion for Judgment as a Matter of Law filed by Defendant (now Wyeth) American Home Products Corp. Motion for Judgment as a Matter of Law. Documents filed: Wyeth's Mo. for Judgment as a Matter of; Law; Attachment.

MPR 17) Motion for Judgment as a Matter of Law filed by Defendant (now Wyeth) American Home Products Corp. Motion for Judgment as a Matter of Law. Documents filed: Wyeth's Mo. for Judgment as a Matter of; Law; Attachment.

Jury Trial held. GWC/RP.

Entry Order by Judge Geoffrey W. Crawford: Jay Young, Court Reporter.

03/12/04 3 documents filed by Attorney R. Joseph O'Rourke for party 2: Wyeth's supplemental proposed Jury; instructions; Certificate of Service. 1 document filed by Attorney Richard I. Rubin for party 1: Proposed Jury Instructions.

2 documents filed by Attorney R. Joseph O'Rourke for party 2: Wyeth's Supplemental Preliminary; Proposed Jury Instructions.

Jury Trial held. GWC/RP.

Entry Order by Judge Geoffrey W. Crawford: Jay Young, Court Reporter.

Verdict reached for the Plaintiff, $7.4 million.

Dispute 1 disposed: Judgment for Plaintiff—Jury Trial.

03/17/04 Entry Order by Judge Geoffrey W. Crawford: See Judgment Order dated 3/17/04.

Copies of Order mailed to counsel letter sent to Plaintiff Diana Levine and Defendant (now Wyeth) American Home Products Corp. and Co-counsel for Defendant Daniel S. Pariser and Co-counsel for Defendant Cara M. Petersen and Co-counsel for Defendant Peter T. Grossi, Jr.

* * *

04/16/04 MPR 19) Motion for Judgment (Renewed) as a Matter of La filed by Defendant (now Wyeth) American Home Products Corp. Motion for Judgment (Renewed) as a Matter of La. Documents filed: Renewed Mo. for Judgment as a matter of; law; Memorandum in support of Mo; attachments; Certificate of Service.

MPR 20) Motion for New Trial filed by Defendant (now Wyeth) American Home Products Corp. Motion for New Trial.

Documents filed: Mo. for New Trial on Damages; Memorandum in support of Mo; attachments; Certificate of Service.

05/20/04 Party 1 filed response to MPR 19.

Party 1 filed response to MPR 20.

1 document filed by Attorney Richard I. Rubin for party 1: Transcripts (5) binders.

MPR's 19-20: 19)Motion for Judgment (Renewed) as a Matter of La; 20) Motion for New Trial given to Judge Geoffrey W. Crawford.

06/07/04 Party 2 filed response to MPR 20.

* * *

08/02/04 Decision on Motion for Judgment Under VRCP 50 filed.

MPR 2-3 status changed to denied.

Copies of Order mailed to counsel letter sent to Plaintiff Diana Levine and Defendant (now Wyeth) American Home Products Corp. and Co-counsel for Defendant Daniel S. Pariser and Co-counsel for Defendant Cara M. Petersen and Co-counsel for Defendant Peter T. Grossi, Jr.

* * *

09/01/04 Notice of Appeal & $225.00 filing fee filed by Atty O'Rourke.

* * *

10/06/04 Order Amending Rule 50 Decision filed.

Copies of Order mailed to counsel letter sent to Plaintiff Diana Levine and Defen-

dant (now Wyeth) American Home Products Corp. and Co-counsel for Defendant Daniel S. Pariser and Co-counsel for Defendant Cara M. Petersen and Co-counsel for Defendant Peter T. Grossi, Jr.

Pltf's 9/7/04 letter and Court's 10/6/04 Order forwarded to Vt. Supreme Court.

10/30/06 Entry Order filed by Vermont Supreme Court affirming decision.

12/11/06 Copy of Entry Order filed by Vt. Supreme Court: "Appellant has filed a timely motion for reargument of this court's October 27, 06 decision in the above matter. Insofar as appellant has failed to demonstrate that the court overlooked or misapprehended points of law or fact that would have affected the result, the motion is denied. VRCP 40.

12/18/06 Entry Order filed by Supreme Court advising motion for reargument is denied.

* * *

01/25/07 Entry Order filed by VT Supreme Court: "The mandate in the opinion issued by this Court on October 27, 2006 is stayed pursuant to the parties' stipulation entered into on January 16, 2007. As agreed in the stipulation, the stay will expire upon either the United States Supreme Court's denial of appellant's petition for a writ of certiorari or, if the writ is granted, affirmance of this Court's decision.

* * *

SUPREME COURT OF VERMONT

2004-384 Heard

Printed: Mon May 12 2008 at 10:16:49
From Washington Superior Appeal Civil
Orig. Dkt. # 670-12-01 Wncv
Judge(s) ; Crawford G; Cook A; Teachout M

DIANA LEVINE, Appellee,

v.

WYETH*, Appellant.

	Date Due	Filed/ Waived	Prog Order Issued
Filed in Trial Court OR Board:		09/01/2004	
Notice of Appeal:		09/07/2004	
Trans. Ordered:	09/15/2004	11/11/1111	
AA Docking Stmt:	09/15/2004	09/17/2004	
AE Docking Stmt:	10/01/2004	09/20/2004	
Record Complete:	11/10/2004	09/17/2004	
Appellant Brief:	11/19/2004	11/22/2004	Yes
Appellee Brief:	01/18/2005	01/21/2005	Yes
Considered on:	10/05/2005	Argued	
Decided:	10/27/2006	cwoj	aff

Counsel for 2004-384
Appellee's Attorney(s)
1096 Rubin, Richard, I.
Appellant's Attorney(s)
975 O'Rourke, R., J.
100 Pro Se

DOCKET ENTRIES for 2004-384

* * *

09/07/2004 Notice of Appeal received. Original notice filed in trial court 09/01/2004. Entry fee paid by American Home Products. Case file (in large box) and docket entries rec'd from tc. TC will retain exhibits until requested.[1]

* * *

01/20/2005 Complied AAB filed by Atty. Keyes.

01/21/2005 AEB & SPC fi by Atty. Rubin.

02/08/2005 ARB fi by Atty. Keyes.

* * *

10/05/2005 Transcripts rec'd from Atty. Keyes—3/8/04 (3 volumes), 3/9/04 (2 volumes), 3/10/04, 3/11/04 and 3/12/04.

HEARD BY FULL COURT. PLR, JAD, DRJ, FWA and Walter Morris. Attys Keyes and Rein and Rubin argued.

* * *

---

[1] Clerk's notations indicating name of person who added docket entry deleted.

10/27/2006 ENTRY ORDER; PLR, JAD, DRJ, FWA and Morris, D.J.; Johnson author, Reiber dissenting: Affirmed. cc of EO and opinion to counsel, trial court, trial judge.

* * *

11/13/2006 Motion for Reargument fi by Atty. Keyes. CC'd Attys. Rubin, Pariser, Wiley, Rein & Felding.

* * *

12/11/2006 ENTRY ORDER. PLR, JAD, DRJ, Walter K. Morris, Jr. and Frederic W. Allen. Appellant has filed a timely motion for reargument of this Court's 10/27/06 decision in the above matter. Insofar as appellant has failed to demonstrate that the Court overlooked or misapprehended points of law or fact that would have affected the result, the motion is denied. cc of EO to counsel and tc.

12/14/2006 Wyeth's Motion to Stay Issuance of Mandate Pending Application to the US Supreme Court for Disposition of Writ of Certiorari fi by Atty. Keyes, cc'd Attys. Rubin and Pariser.

12/19/2006 Ms. Levine's Response to Wyeth's Motion to Stay Mande fi by Atty. Rubin, cc'd Atty. Keyes.

12/22/2006 Wyeth's Reply in Support of its Motion to Stay Mandate fi by Atty Keyes, cc'd Attys. Rubin and Pariser.

* * *

01/19/2007 Stipulation Regarding Conditions of Stay filed & signed by Attys. Keyes & Rubin. Gate to EAM.

01/23/2007 ENTRY ORDER. DRJ. The mandate in the opinion issued by this Ct. on 10/27/06 is stayed pursuant to the parties' stip. entered into on 1/16/07. As agreed in the stip., the stay will expire upon either the US Supreme Court's denial of appellant's petition for a writ of certiorari or, if the writ is granted, affirmance of this Court's decision. cc of EO to counsel and tc.

* * *

01/22/2008 Ltr. rec'd from the US Supreme Court. The Petition for a Wit of Certiorari is granted. Petitioner's brief is due 2/25/08, respondent's brief is due 3/24/08 and ARB is due according to the rules of the US Supreme Court.

* * *

STATE OF VERMONT
WASHINGTON COUNTY, SS.

DIANA LEVINE	)	
	)	WASHINGTON SUPERIOR
v.	)	COURT
	)	DOCKET NO. 670-12-01 Wnev
WYETH	)	

AMENDED COMPLAINT

Diana Levine says:

1. Diana Levine lives in Marshfield, Vermont and on April 7, 2000 was patient at the Health Center in Plainfield, Vermont.

2. On April 7, 2000, she went to the Health Center complaining of migraine headache and received an intravenous injection of Phenergan®, which was manufactured by the defendant, American Home Products (AHP).

3. AHP is a pharmaceutical company and sells its products, including Phenergan®, in Vermont.

4. Diana Levine was given the contents of two 25 mg tubex' of Phenergan®, which were transferred intravenously into the antecubital space of her right arm without further dilution.

5. The Phenergan® given to Diana Levine was defective. The product information failed to instruct the clinician administering the drug to dilute the drug; it also failed to instruct the clinician to administer the drug through a running IV. The product information also failed to provide sufficient and adequate warnings that intra-arterial injection or extravasation could cause irreversible gangrene and loss of limb. The

Phenergan® was not reasonably safe due to inadequate warnings and instructions regarding foreseeable risks of harm.. If adequate instructions concerning the proper administration and dilution of Phenergan® had been provided to health care providers known to administer the drug intravenously, the physician's assistant administering the IV would have taken appropriate measures to reduce the risks of harm in accordance with the warnings and instructions.

6. The Phenergan® sold by the defendant is also not reasonably safe for intravenous administration because the foreseeable risks of harm posed by the intravenous administration of the drug are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health care providers, knowing of such foreseeable risks and benefits, would not prescribe the drug intravenously for any class of patients.

7. The clinician at the Health Center inadvertently administered the drug into an artery, or into the tissue outside the intended vein (extravasation). Such an occurrence is a forseeable consequence of IV drug administration.

8. As result of the defective drug, Diana Levine suffered extreme pain, suffering, two amputations of her right arm (the second midway between the wrist and elbow), loss of livelihood, and extreme emotional anguish.

9. Diana Levine is musician. She can no longer play the bass guitar and piano. She had a successful music production business which is no longer viable.

10. The defendant has known since 1987 that its instructions were inadequate and unsafe insofar as they stated that Phenergan could safely be administered intravenously without using a running IV. A running IV

is an intravenous administration method which utilizes a bag of saline suspended above the patient and connected by means of an indwelling catheter to the patient's vein. The saline in the bag will flow by gravity through plastic tubing into the vein. Medication can be administered through a side port in the tubing into the flowing saline, or added to the bag of saline itself.

11. In 1988, the defendant prepared new instructions for its product insert which made clear that Phenergan must be administered intravenously only through a running IV in order to ensure adequate dilution and guarantee venous placement.

12. The defendant has known for more than 25 years of the grave risks associated with inadvertent arterial injection or extravasation of Phenergan, including irreversible gangrene and amputation.

13. The defendant knew, from at least 1988, that instructions requiring administration of Phenergan intravenously only through running IV could prevent inadvertent arterial injection and extravasation along with its catastrophic results.

14. From 1988 through 2000, the defendant was aware that inadvertent arterial injection and extravasation continued to cause severe injury to patients receiving Phenergan intravenously.

15. Wyeth stated on multiple occasions:

> When implemented this [revised] warning will incorporate the "best thinking" of both Wyeth-Ayerst and the division in regard to prevention of misinjection should it occur. Since misinjection may cause severe tissue injury (including necrosis with resultant gangrene and amputation) we believe that the use of the updated

warning is of critical importance for the safe use of Phenergan injection.

16. Despite its knowledge of the continued occurrence of injury and the fact that revised instructions would lessen or completely avoid the harms associated with intravenous administration, the defendant chose not to revise its product insert and instructions.

17. The defendant had a duty to revise its product insert to prevent the foreseeable harm that would occur upon misinjection.

18. If the defendant had revised its instructions to require that Phenergan only be administered through a running IV, the injury to Diana Levine would not have happened. The failure to revise the instructions was the proximate cause of her injury.

19. The conduct of the defendant was negligent, grossly negligent, wanton, willful, and totally unjustified.

20. The negligence and/or gross negligence was the proximate cause of the plaintiff's injuries.

WHEREFORE, Diana Levine seeks appropriate damages for her loss.

Dated at Barre, Vermont this 18 day of December 2003.

Respectfully submitted,

DIANA LEVINE

By: /s/ _____

Richard I. Rubin, Esq.

STATE OF VERMONT
WASHINGTON COUNTY, SS.

Diana Levine Plaintiff,	))
v.	) Washington Superior Court) Docket No. 670-12-01 Wncv
American Home Products, Inc. (now Wyeth), Defendant.	)))

Stamp: FILED
(initials)
2003 DEC 23 P 1:08
SUPERIOR COURT
WASHINGTON COUNTY

Decision re: Wyeth's Motion for Summary Judgment

Plaintiff Diana Levine alleges that she suffered harm from the improper administration of a drug which itself was caused by insufficient warnings on the drug's label. Defendant Wyeth, manufacturer of the drug, has filed a motion for summary judgment. Defendant is represented by Peter T. Grossi, Jr., Esq. Plaintiff is represented by Richard I. Rubin, Esq. For the following reasons, Wyeth's motion for summary judgment is denied.

The basic facts of this case are undisputed. Plaintiff has a long history of suffering debilitating migraine headaches. As she had done many times previously, on April 7, 2000, Plaintiff visited Northeast Washington County Community Health, Inc. (the Health Center)

for treatment of an episode. A nurse acting on the instruction of a physician assistant gave Plaintiff an intramuscular injection of Demerol (for pain) and Phenergan Injection (for nausea). Though this combination had provided relief in the past, on April 7 it was ineffective. Plaintiff returned to the Health Center later in the day.

Jessica Fisch, a physician assistant, treated Plaintiff on her return. Fisch decided to administer a second dose of Demerol and Phenergan Injection. However, rather than injecting it intramuscularly as Plaintiff typically received it, Fisch attempted to inject the medication intravenously using a "butterfly infusion set." Fisch inadvertently injected the medication into an artery rather than the intended vein. The parties do not dispute that this inadvertent intra-arterial injection of Phenergan caused the necrosis and gangrene that led to the amputation of Plaintiff's arm just below the elbow. The parties also do not dispute that the FDA approved label for Phenergan plainly discloses the high risk of necrosis and gangrene leading to amputation if Phenergan is inadvertently injected intra-arterially. Other facts are mentioned below as necessary

Plaintiff claims that the warnings in the label about intra-arterial injection of Phenergan are inadequate and that inadequacy proximately caused Plaintiff's injuries. The allegations of inadequacy focus primarily on whether intravenous injection is appropriate in any circumstances at all, and if so, how precisely it must be done to obviate the extreme risk of harm attending intravenous injection. Denying any inadequacies in these regards, Wyeth asserts three grounds for summary judgment: 1) the "failure to warn: claim is pre-empted by the supremacy of federal law; 2) there is no proximate causation; and, in any event, 3) Plaintiff's claim for

punitive damages lacks of any evidentiary support. On the current record, the court cannot conclude that Wyeth is entitled to judgment as a matter of law with regard to any of these issues.

Preemption

Plaintiff asserts two preemption arguments: field preemption and conflict preemption. Field preemption refers to instances where state law "regulates conduct in a field that Congress intended the Federal Government to occupy exclusively," whereas conflict preemption refers to situations where "it is impossible for a private party to comply with both state and federal requirements." Motus v. Pfizer Inc., 127 F.Supp.2d 1085, 1091 (C.D.Cal 2000) (quoting English v. General Elec. Co., 496 U.S. 72, 78-79 (1990)). The two theories often overlap. Wyeth makes both overlapping arguments, which the court addresses separately.

With regard to field preemption, Wyeth argues that the FDA's regulatory activity is so extensive with regard to the content of drug labels that state tort law actions asserting failure to warn claims effectively are preempted as a matter of law. Wyeth concedes that nearly all cases addressing this issue have concluded that the FDA;s drug labeling activity sets a floor, not a ceiling, on the strength of the language in the labeling, and hence preemption usually does not occur. See Wyeth's Memorandum of Points and Authorities at 14 n.4 (filed May 15, 2002). Nevertheless, Wyeth argues that cases so holding are outdated in light of recent United States Supreme Court cases such as Buckman Co. v. Plaintiffs' Legal Committee, 531 U.S. 341 (2001). After carefully reviewing the authorities, the court is persuaded that neither Buckman nor other United States Supreme Court cases compel the conclusion

urged by Wyeth and that the exhaustive analyses in lower federal court cases rejecting preemption—such as Caraker v. Sandoz Pharmaceuticals Co., 172 F.Supp.2d 1018, 1030-1044 (S.D. Ill. 2001) and Motus, 127 F.Supp.2d at 1091-1100—are valid and sound. The court adopts the reasoning of Caraker and Motus and rejects Wyeth;s field preemption argument.

Wyeth also argues that the facts specifically relating to this case demonstrate an actual conflict between a specific FDA order with which it was obligated to comply and Plaintiff's failure to warn action. There is evidence suggesting that Wyeth at least at one time may have considered strengthening the label warning with regard to intra-arterial injection. In that regard, Wyeth has submitted a document dated August 22, 1988 denominated "Amplification of Draft Labeling Submitted May 3, 1988." Appendix to Wyeth's Memorandum of Points and Authorities. The document includes notes on a Phenergan label with ostensibly proposed revisions including stronger language about intra-arterial injection. Wyeth then cites to a February 21, 1997 letter from the FDA to Wyeth regarding your "supplemental new drug application dated September 21, 1981 ... for Phenergan (promethazine hydrochloride) Injection. Appendix G to Wyeth's Memorandum of Points and Authorities. The following sections are relevant:

> We have completed the review of this supplemental application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as follows.
>
> > The following comments are provided regarding the version of the Phenergan Tubex and

> Ampul labeling submitted in the August 6, 1996 amendment. Please note that the term "current labeling" refers to these versions.

The tenth numbered section of comments states, in relevant part:

> 10. The WARNINGS section should be modified to read as follows.
>
> SULFITE SENSITIVITY—
>
> ...
>
> f. **Inadvertent Intra-arterial Injection**—Retain verbiage in current label.

Without any evidentiary basis other than the two documents mentioned above, Wyeth argues that the phrase "Retain verbiage in current label" foreclosed any possibility of incorporating into the label the sort of stronger warning that Plaintiff urges was necessary, and that appears more or less in the notes on the August 22, 1988 document.

On this record, Wyeth's analysis is highly speculative at best. The February 21, 1997 letter specifically states that the term "current labeling" refers to the "labeling submitted in the August 6, 1996 amendment." Wyeth however asserts that the expression "current label" in paragraph 10(f) refers to the labeling then in effect, rather than the labeling in the August 6, 1996 amendment. Wyeth later clarifies that the labeling in the August 6, 1996 amendment is the same as the labeling then in effect. Whatever the truth may be, the record includes no evidence of any kind implying that the expression "Retain verbiage in current label" has the dual meaning Wyeth advances: that the "current" language must be retained while the language proposed in the August 22, 1988 document is forbidden. As a more

general matter, no record evidence suggests that Wyeth earnestly attempted to alter the label to strengthen the warning about intra-arterial injection, and that the FDA specifically disallowed the strengthened language. The record as currently developed lacks any evidence that the FDA set a ceiling on this matter. Accordingly, the court discerns no basis for conflict preemption.

Proximate Causation

Assuming arguendo that the warnings in the label were inadequate as alleged, Wyeth argues that Plaintiff will not be able to prove that the inadequacy proximately caused the harm. Wyeth's argument is straightforward: even if the label included different instructions, Fisch would not have followed them. Plaintiff asserts the contrary and argues that the issue should be reserved for the jury.

The Vermont Supreme Court adopted strict products liability as embodied in Restatement (Second) of Torts § 402A in Zaleskie v. Joyce, 133 Vt. 150, 154-55 (1975). Consistent with § 402A, the Vermont Supreme Court adopted the so called "read and heed" rule in failure to warn cases. :Where warning is given, the seller may reasonably assume that it will be read and heeded; and product bearing such a warning, which is safe for use if it is followed, is not in defective condition, nor is it unreasonably dangerous." Restatement (Second) of Torts § 402A cmt. j. "In effect, a presumption of causation is created in failure-to-warn cases. This does not impose absolute liability on the manufacturer, but merely shifts the burden to the manufacturer to go forward with the evidence." Menard v. Newhall, 135 Vt. 53, 54-55 (1977). Both parties causation arguments presume the applicability of the read and heed rule to

this case.[2] Wyeth seeks to overcome the presumption of causation with evidence that Fisch disregarded the label's warning and thus would have disregarded any strengthened warning.

While Wyeth's argument is not without meaningful evidentiary support, competing evidence also supports a contrary conclusion. The court need not dwell on the atomies of that dispute here, however; it is sufficient to document its existence in light of Wyeth's burden. Additionally, as is common in this type of case, the issue of the adequacy of the warning and the issue of causation overlap. See Town of Bridport v. Sterling Clark Lurton Corp., 166 Vt. 304, 310 (1997) (adequacy and causation "closely intertwined"). Plaintiff has come forward with evidence sufficient to foreclose judgment as a matter of law on the issue of adequacy of the warning. Both issues therefore must be resolved finally by the jury. See id, at 311 ("ordinarily the sufficiency of [the] warning is a question for the jury).

Punitive Damages

Lastly, Wyeth argues that Plaintiff's claim for punitive damages should be dismissed for lack of any evidentiary support whatsoever. Plaintiff responds to this argument by asserting without any evidentiary support that the court should assume for purposes of the summary judgment decision that Wyeth maliciously refused to alter the Phenergan label for the sole purpose of maximizing profits in patent dereliction of patient

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[2] At least some courts have held that in certain circumstance the read and heed rule does not create a presumption of causation in failure to warn cases against pharmaceutical manufacturers. See, e.g., Motus v. Phizer Inc., 196 F.Supp.2d 984, 992-94 (2001).

safety. The court declines to draw such an inference without evidentiary support. Nevertheless, the development of evidence which could support punitive damages appears at least to be possible. "Before the court can apply the law, it must have an adequate factual basis for doing so." 10A C. Wright & A. Miller, Federal Practice and Procedure § 2725, at 412. Judgment on this issue is premature at this time.

Order

For the foregoing reasons, Wyeth's motion for summary judgment is DENIED.

Dated at Montpelier, Vermont this 23rd day of December, 2003.

/s/_____
Alan W. Cook
Superior Court Judge

STATE OF VERMONT
WASHINGTON COUNTY, SS.

DIANA LEVINE Plaintiff v. AMERICAN HOME PRODUCTS, INC. (now) WYETH Defendant	Washington Superior Court Docket No. 670-12-01 Wncv

ANSWER OF DEFENDANT WYETH TO PLAINTIFF'S AMENDED COMPLAINT

COMES the Defendant, Wyeth, by its attorneys and respectfully answers the Plaintiff's Amended Complaint and says as follows:

1. Wyeth has no particular information as to the allegations in Paragraph 1 and therefore denies the same and leaves the Plaintiff to her proof.

2. Wyeth has no particular information as to the allegations in Paragraph 2 and therefore denies the same and leaves the Plaintiff to her proof.

3. Wyeth admits Paragraph 3.

4. Wyeth has no particular information as to the allegations in Paragraph 4 and therefore denies the same and leaves the Plaintiff to her proof.

5. Wyeth has no particular information as to the allegations in Paragraph 5 and therefore denies the same and leaves the Plaintiff to her proof.

6. Wyeth denies Paragraph 6.

7. Wyeth has no particular information as to the allegations in Paragraph 7 and therefore denies the same and leaves the Plaintiff to her proof.

8. Wyeth has no particular information as to the allegations in Paragraph 8 and therefore denies the same and leaves the Plaintiff to her proof.

9. Wyeth has no particular information as to the allegations in Paragraph 9 and therefore denies the same and leaves the Plaintiff to her proof.

10. Wyeth denies the allegations in the first sentence of Paragraph 10. Wyeth states that there are a variety of methods of intravenous administration including by use of a bag of saline suspended above the patient and connected by means of an indwelling catheter to the patient's vein, which will flow by gravity or by mechanical means. Wyeth otherwise denies the remaining allegations in Paragraph 10.

11. Wyeth denies the allegations in Paragraph 11.

12. Wyeth states that it has known of the risks associated with inadvertent intra-arterial injection of Phenergan® Injection for many years and that it has adequately warned of those risks during all relevant time periods. Wyeth otherwise denies the allegations in Paragraph 12.

13. Wyeth denies the allegations in Paragraph 13.

14. Wyeth denies the allegations in Paragraph 14.

15. Wyeth admits that the language quoted in Paragraph 15 of Plaintiff's Amended Complaint appeared in Annual Reports for Phenergan® Injection submitted to FDA for the years 1989 through 1995. Wyeth further states that the allegations in Paragraph 15 seek to characterize writing, to which no response is required, but, if response is deemed necessary, Wyeth states that the referenced writing speaks for itself and any attempt to characterize the writing is expressly denied.

16. Wyeth admits that it did not adopt the draft labeling changes submitted to FDA on May 3, 1988, referenced at Exhibit 4 to Plaintiff's Motion to Amend Complaint (NDA 00005337-00005348). Wyeth otherwise denies the allegations in Paragraph 16.

17. Wyeth states that Paragraph 17 states a legal conclusion to which no response is required, but, if a response is deemed necessary, Wyeth denies the allegations in Paragraph 17

18. Wyeth states that Paragraph 18 states a legal conclusion to which no response is required, but, if a response is deemed necessary, Wyeth denies the allegations in Paragraph 18.

19. Wyeth states that Paragraph 19 states a legal conclusion to which no response is required, but, if a response is deemed necessary, Wyeth denies the allegations in Paragraph 19.

20. Wyeth states that Paragraph 20 states a legal conclusion to which no response is required, but, if a response is deemed necessary, Wyeth denies the allegations in Paragraph 20.

FIRST SEPARATE AND COMPLETE DEFENSE

The Complaint fails to state claim upon which relief can be granted at the Washington Superior Court.

SECOND SEPARATE AND COMPLETE DEFENSE

The Defendant says that the Plaintiff herself was negligent and/or any intervening parties were negligent, which negligence is expected to be determined through discovery. The Plaintiff and/or the Interveners' negligence was greater in kind and degree than any negligence on the part of the Defendant, which negligence on its part, it denies, and because of the Plaintiff's negligence and/or the Interveners' negligence, Plaintiff cannot recover against the Defendant.

THIRD SEPARATE AND COMPLETE DEFENSE

Plaintiff's alleged injuries and damages were not proximately caused by any act or omission by Defendant.

FOURTH SEPARATE AND COMPLETE DEFENSE

The damages alleged by Plaintiff were caused or proximately caused by some person(s) or third party other than Defendant and for whom Defendant is not legally responsible.

FIFTH SEPARATE AND COMPLETE DEFENSE

Plaintiff's claims, including but not limited to Plaintiff's claim for punitive damages, are barred in whole or in part by the doctrine of federal preemption.

DEMAND FOR JURY TRIAL

The Defendant demands Jury Trial on all issues.

Dated at Washington, D.C. this 31st day of December, 2003.

WYETH

By: /s/_____

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EXCERPTS OF TRIAL TRANSCRIPT, NO. 670-12-01 (VT. SUPER. CT.)

MARCH 8, 2004

* * *

[Conference on Motions in Limine]

[8] agree that arterial injection is a no-no.

MR. RUBIN: Well, the issue in the case is instructions, not that this can happen.

THE COURT: Right.

MR. RUBIN: And over the course of 30 years there have been multiple amputations, gangrene, untoward events that have gone on continually since at least 1969 with this product. And these reports are in the FDA database available to the company, of course, many of which we got from the company itself when we requested the Adverse Reports that they had in their files. There's also literature in their files, articles, internal memos that talk about amputations and other untoward events.

Our claim is that this drug should not be introduced intravenously at all. And it's really important that as a basis of our experts' opinion that they looked at these Adverse Reports and, although the company says in its warnings watch out if it gets in an artery, you can have gangrene, the extent and degree to which this is known, the frequency that it happens, the severity of the result are all important for their determination that this drug is not safe to be used

* * *

[Opening Statement of Richard I. Rubin, Counsel for Plaintiff]

[39] arm. It's a case about Wyeth the drug company that manufactured this drug Phenergan. You'll hear a lot about Phenergan. It's a case about Wyeth, who knew that this drug was one hundred percent safe if injected in the butt intramuscularly, but they also know it posed a great risk of amputation and loss of limb if it was introduced intravenously. And it's a case about Wyeth. They had the obligation to publish instructions that would prevent this from happening. And there was a simple instruction that they could have written "Do not use this drug intravenously."

That's what the case is about. We'll have a number of experts, doctors, to tell you why is this so? Let me tell you a little bit about Diana. As I said, she lives in Marshfield. She's lived in the same house for 27 years. This accident, this tragedy, happened in April of 2000. Diana is a mother. Her daughter Jessie is here. She's a musician, highly accomplished musician. I'll talk about that more in a minute. Community member, a family member, her brother is here seated there in the tie. She was raised in upstate New York. She went to Glens Falls High School. Then she went to UVM.

* * *

[45] want to give it, but she gave it intravenously in a method that she had used 50 to 75 times before.

Now, we're going to talk about medicine and stuff and a little bit about needles. So one of the jurors—if you have any squeamishness about needles, let us know. But the science isn't complicated. It's really pretty straightforward and common sense. She gave the intravenous injection by using what's called a single

dose infusion. It's like the needle that they use to draw blood, a small needle that goes in the vein in the crook of your arm. It has a rubber hose, a tube on the back of it, and you attach that to a syringe, about three cc's of liquid, slowly load that up with your Phenergan and you slowly over two minutes push that out of the syringe a little tube through the needle which is in the vein hopefully into your arm. That's called a direct intravenous injection. IV push injection. Very common.

At the time it was given at the Health Center this way, it was a standard use of an intravenous injection and that's how it was given at Central Vermont Hospital. There is another way to give an intravenous injection that may be more common to you and that's what you see—or you've [46] had in the hospital when you have a bag, you know, on a hook and you put the tube running down the bag. And what they do is they set up the IV by putting in a soft, flexible tube or catheter and they put that in your vein and then they attach that to the tube. You've all seen that. And then they let the clear liquid saline. It's saline. They let that run and this runs down the tube through the catheter into your vein. And they let it run because it's harmless. And they let it run a couple of minutes. If it's running, they know they're in the vein because the pressure—if they're in the artery where you do not want to be, if it runs into the artery, it will back up because the pressure in the artery, you know, if you cut an artery, it spurts, so the pressure in the artery will stop—literally stop the flow of this saline from running. So if you're in the artery, it won't run. If you pierce the back of the vein so that it's under—in the tissue, which you don't want to happen because then it can bathe the artery and cause this disaster, it will form a puddle in your skin and stop running.

So if you use this flow- free-flowing IV, that's how I'll refer to it, you can be pretty [47] sure—much more sure that you will not be putting this corrosive, dangerous drug into a vein.

So first she sets up, she gets the equipment, she gets the needle for this direct infusion, she gets the—and she slowly over two minutes administers the Phenergan into the artery. She unhooks the syringe, takes a little saline, pushes that through to clear the line. She took another syringe and puts in the Demerol. Standard practice. And the practice was consistent with the instructions that were provided by Wyeth.

Now, when a drug company sells a product that's going to be administered at a hospital they have to tell the people who are administering the product how to do it. And if they can avoid risks that they know of, they have to write instructions that will avoid those risks, even if one of the risks is that the clinician might make a mistake. If they know that that can happen, and they can simply fix the problem with no significant impact on the effectiveness of the drug, they'd better do it.

She administered this drug the way she had done it before and consistent with the instructions and what happened? The drug got out [48] of the vein, bathed the artery or went directly into the artery, was corrosive, caused this spasm in the artery, the spasm spread down her forearm into her fingers. There were spasms in the little vessels, the little arteries, clots, her tissue died, she got gangrene and ultimately she lost her arm.

When she came back—she went home again, the Demerol knocked her out, she went back at four o'clock in the afternoon. Her headache was gone, but her arm was killing her and she said help me. John Matthew, who will testify, was the doctor at the Health Center.

He's actually seated in the back. He said we've got to deal with this. This is serious. So he had one of his people call Wyeth because they have a phone number where you call if there is a problem. And he called them and they said—talked to some woman there, some, you know, there's this problem with the arm swelling, and it's changing colors and it's cold. What do we do? And they said I don't know. We'll send you a form to report it. So they called the vascular surgeon up in Burlington and he said there's probably nothing you can do. You can try blood thinners, you can try this, you can try that.

* * *

[53] irreversible gangrene and loss of limb if it gets into an artery. They may say it in their warnings, and you'll hear, oh yes, we say it, but they have known for 30 years that if it leaks out of a vein it will cause tissue death, gangrene.

They've also known for 30 years that this rigid needle that was used, that butterfly system that was used by Jessica Fisch, causes extra problems. And we have memoranda from their files where they—where they talk about use of these rigid needles, these needles as opposed to the floppy catheter from the free-flowing IV, causes this—it's more likely to happen because you don't have a safety monitor and it can leak out of the vein.

They've also known for 30 years—and this is not in their warnings—that some significant percentage of us have what we call abberant arteries. Arteries in the wrong place. We're all not the same inside. There's two—three to 12 percent of us that have arteries artifically shouldn't be there. Shouldn't be there. They are where they are, but they're not normal. Three to 12

percent of us have these little vessels. Some are very close to the

* * *

[55] MR. O'ROURKE: Your Honor, this is getting into argument rather than opening statement.

THE COURT: I think that's probably a fair comment. Why don't we stick just to the facts.

MR. RUBIN: The evidence will show that Jessica Fisch, even if she was responsible, even if she made a mistake, they will say that she didn't stop when Diana may have complained of some pain when the injection was going in. The evidence will show that it probably was too late at that point.

They will also—it's also the case that since they have known for 30 years that clinicians make mistakes, that they could have fixed this problem by changing the instruction to preclude intravenous use. You'll also hear that this drug was approved by the federal Food and Drug Administration. But the evidence will be that what happens is the Food and Drug Administration relies on the drug companies to make its decision. They get their information from the drug companies, review this information, and then sign off on the labels. The approval by the Food and Drug Administration is the minimum federal standard for [56] the sale of the drug.

The court will tell you that it is your decision that you are the judges of whether the instructions in this case are safe and the product was defective or whether the company was negligent.

I want to conclude by talking a little bit about damages. We will ask for a very large amount of money here. And there's two parts to the damages. There's

kind of the economic, the numbers that we can put up on a board, and we will put up. And we will show you that the loss of her business and her ability to earn an income—we'll have experts to testify to this—over the course of the rest of her working life is approximately $600,000. And we will offer evidence that there's $225,000 roughly in medical bills and other expenses so far. And we have a Life Care Plan, which has been developed, will show what she will need for the rest of her life to at least to try and make a physical accommodation for what happened to provide therapy is about another million dollars. And these numbers are not seriously in dispute. And they total roughly $2 million. But that's the easy part.

You will also be asked to compensate

* * *

[Testimony of Dr. John Matthew]

[79] roughly?

A Yes. She was seen on that day by both Dr. Sandy Craig, who is another physician in our office, and by myself, but from that point forward—there were occasions when she saw someone else in the office, but I was supervising her care doing probably 90 or better percent of the dealing with physician's assistants and with her in the interval until she ended up being transferred to Dartmouth.

Q I'm going to ask you in a few minutes to kind of show the jury some of the equipment that is routinely used with this injection, but why don't you just take us through your understanding from the medical records of what was done.

A I think—

Q Starting in the morning when she got the first—

A When she came in the morning she saw a physician's assistant, Kim Pierce, as I recall. She had an injection, intramuscular injection of a hundred milligrams of Demerol and 50 milligrams of Phenergan.

Q Could you explain what the Demerol—I mean you heard my opening, but we have to hear from you. I'm not sure it's disputed. What does the [80] Demerol do?

A Demerol is for pain and we're trying to stop her headache. Phenergan is for — often migraines have associated vomiting or retching or nausea. The Phenergan is for sedation and nausea. Sleep can break a migraine so sedative value. It has an anti-nausea value. And Demerol itself can cause or aggravate nausea and vomiting so it prevents that side effect of the Demerol that you're using for pain.

Q Is that why you give them together?

A Yes.

Q Was the decision to give the Phenergan and the Demerol intramuscularly in the butt appropriate in the morning?

A I think it was entirely appropriate.

Q Then what happened? Did it cure the migraine?

A I gather that she went to a friend's house and slept, but she came back with the headache quite bad as I understand it, retching and she looked wretched. I saw her walk in and go down the hall and then get placed into a room that day and she looked quite terrible. She was holding her head.

[81] Q You actually remember that?

A Oh, she looked terrible.

Q Go ahead.

A So what transpired subsequently, she is in an exam room. A lot of people have migraine photophobia where light hurts. They turned down the lights, put an exam spotlight on the situation. When they got to the IV point, she was given an injection, Imitrex, which is a drug that can break a migraine. It failed to do that. I then understand that Jessica got the Phenergan, the contents of two—there is—there is a kind of injection device called a Tubex, which is like a preloaded cylinder that can go into a mechanism and become a shot. That's the only way we had Phenergan available at that time. The contents of two 25 milligram Tubexes, each having one cc, and 25 milligrams were unloaded from the Tubex and put into a three cc syringe.

Q We'll demonstrate this in a minute. Go ahead.

A She then had—Jessica then placed this butterfly IV infusion set needle in Diana's vein, having tied her arm to make the veins pop up. We chose to use butterflies in the situation—[82] butterfly needle because it can be kept quite superficial and it's short.

Q Why don't you stop. I think it might be best if I actually use some of these devices as you're going through this.

A Okay.

(Bench Conference)

MR. RUBIN: I was here in December. There was one woman in the front who has a very strong negative reaction to needles. You can see it on her face. You might ask to switch positions so she can sit in the back

row. She actually called Judge Cook last trial. She got through it, but I think it would be a good idea.

MR. O'ROURKE: I have no problem with that, your Honor. Whatever you want to do is fine with me.

(Open Court)

THE COURT: What we're going to do is we'll take our break now, but before I do that is there anybody who's nervous about needles and would like to switch position from the front to the back? They certainly can do it, just let the court officer know that you've done that when we come back so we can make sure that we know where [83] everybody is, okay? Let's take 15 minutes off now and we'll get back together just a few minutes before quarter of.

(Court recessed from 10:28 a.m. to 10:55 a.m.)

Q Before we go through actually the mechanics here, just ask a few more overview questions, Dr. Matthew. Was the decision to give the Phenergan in the afternoon by intravenous injection appropriate?

A I think it entirely appropriate.

Q Why?

A She had failed with IM earlier. Jessica wanted to get a good, higher, immediate concentration of Demerol in terms of relief of the migraine and the Demerol could induce more retching or vomiting and the 50 IM dose of Phenergan earlier had failed to control her nausea. It was a few hours later and she was still retching, so she wanted to get both a quicker, higher concentration of Demerol and an accompanying dose of Phenergan to keep her retching from getting worse and to help it.

Q Why didn't she give—why wouldn't it have been appropriate to give the Demerol intravenously, then give the Phenergan in the butt?

[84] A Because the Demerol would be circulating quickly through her brain and potentially causing her to have vomiting while the Phenergan absorbing IM would be slower and delayed so we might have aggravated her nausea and vomiting.

Q Now, you've reviewed the product insert in this case?

A I have.

MR. RUBIN: By agreement Plaintiff's Exhibit 1 is the product insert. I showed this to counsel before.

MR. O'ROURKE: No objection.

MR. RUBIN: I would offer that.

THE COURT: Okay, one is admitted.

Q I don't want you to try and read it. I want to introduce it, but I want to talk about the dosage. Was the decision to give 50 milligrams of Phenergan an appropriate dosage given the situation?

A I think so. I know that the package insert says that the usual dose is 25 I believe, but it may be used at 50 to 75 milligrams and actually is very commonly used at doses in that range. I should tell you that there are—drugs come out and they have indications that are written [85] in their package insert and they have a set of rules. Oftentimes it's not altered for quite some number of years and over time common practice will often find uses for drugs which are not listed in the initial release of the drug and the dose used or the dose range used may evolve over time. So I don't think it would be in any way unusual to find 50 milligrams to be

used in an emergency room, for example, in similar circumstances.

Q And the method of administration—you started to tell us before the break—was by use of a butterfly infusion set?

A That's correct.

Q What's that? Why don't you come down and actually show us what this is. Exhibit 22, which I've showed to counsel is the—it's a number of different pieces that went together with the—go together with the butterfly infusion sets and I would offer those now.

MR. O'ROURKE: No objection.

THE COURT: That's two.

MR. RUBIN: Twenty-two.

THE COURT: All right.

Q Why don't you—are you okay?

A This is our substitute for an arm. May [86] I take with your asking me a question—

Q Well, I have to ask you one question. What I'd like you to do is to demonstrate based on what the standard procedure and as your understanding what happened in the examining room. Starting first with the—better offer—I can offer all of these at this time. Maybe that will save time.

MR. RUBIN: Exhibit 26, Mr. O'Rourke, is a 3 cc syringe.

MR. O'ROURKE: No objection.

MR. RUBIN: Exhibit 25 is a stand around free-flowing IV setup. Offer that.

MR. O'ROURKE: No objection.

MR. RUBIN: Exhibit 23 is a Tubex, which is not a Phenergan Tubex, but it is an example that's going to be used for illustration as to what generally a Tubex is. It's not offered as the Phenergan Tubex.

MR. O'ROURKE: No objection.

MR. RUBIN: And Exhibit 24 are two ampules or little bottles of promethazine. One is 50 milligrams, and one is 25 milligrams for purposes of illustrating another point in his testimony about how the product is distributed, and [87] it's not claimed that this was used on that date. It's for illustration.

MR. O'ROURKE: No objection.

THE COURT: All right. Twenty-three, 24, 25, and 26 are all admitted.

Q Okay. Getting—done with the housekeeping. Why don't you explain what happened starting with the Tubex first perhaps?

A Illustrate what the Tubex is. Tubex is a preloaded cylinder of a medication which, if it was used to inject with its needle, would be put in a—usually a metal, maybe a plastic, apparatus. It screws on—the plunger screws onto this little screw in the back, a rubber plunger that you can then push the solution as a shot down the barrel. So the Tubex by itself can't function. It goes into a mechanical apparatus. So the Tubex structure by itself cannot be used for an injection. It has to be put into an apparatus. Some of the apparatus might be metal or plastic and they're used to push down the plunger mechanism to make this into an injection.

We don't have a Phenergan Tubex of either 50 or 25 because those are no longer manufactured as I un-

derstand it. So this is another company's Tubex, [88] but it illustrates what Tubex is.

Q Okay. Is there writing on this barrel of the Tubex?

A This is a different medicine and there's the writing that tells about its concentration, its dose, its strength, and it says "For IM use only."

Q Now, that's—

A And a date for the drug outdating and serial number for the drug batch.

Q Now, what happened in this case was the contents of that Tubex was transferred into a syringe, right?

A The contents of two Tubexes. This product, Phenergan, came in two sizes of Tubex. That's all we had in our office at the time were these Tubexes. One would be 50 milligrams in one cc and would say "For IM use only."

Q Let me make sure the jury understands. I'm going to circulate this. It's capped and what—what you're saying is the Tubex for Phenergan has one cc in it?

A Yes, and one strength of it is 50 milligrams in that cc and that's labeled on—the barrel was labeled when it was manufactured "For IM use only," or words very similar to that.

[89] Q How many cc's—this is a Tubex of how many cc's?

A I'll have to look at it to see, probably got marks on the barrel. This has two cc's in it because if you let the air bubble go up, you've got two cc's of liquid.

Q So the Tubex with Phenergan was half that size?

A Half of this volume.

Q And did the Tubex have any writing on it for the Phenergan?

A The Tubex 50 milligrams in one cc I do clearly recall said "For IM use only."

Q What's that mean?

A For intramuscular, shot in the muscle as opposed to IV use only. I'm not certain that the 25 milligrams in one cc, which we used, said IM or IV. I know that it could be used either way, but I don't know if that was on the barrel or not.

Q Okay. So what happens next?

A So Jessica requested a nurse to get her the Phenergan and the nurse would transfer the contents of two 25 milligram—

Q Keep your voice up.

A —per one cc Tubex cartridges into a [90] single three cc syringe with a locking mechanism on the front so that it could be hooked onto the IV infusion device. She's got two in one so-to-speak. The nurse could draw that up in a number of ways. I think in this instance she pierced through the rubber in the back of the Tubex and drew it into the syringe.

Q Wait a second. So this syringe has three cc's or cubic centimeters of—

A Space.

Q —space. And what you do is you take two of those one cc Tubexes and load this up two-thirds full?

A That's correct.

Q Okay. Now, you have your cc—your syringe full of Phenergan, right?

A And she has some normal saline, salt water, and she has some Demerol.

Q This is sterile water?

A We would use saline and it would be drawn up. The top would come up and that would be drawn up in another syringe and she would have Demerol—in this case there was a 50 and a 25 vial used—drawn up into one cc syringe, so she's got three syringes lined up.

[91] Q Okay. So now she's got her three syringes all lined up with 2 cc's of Phenergan in the syringe; which is she going to inject first?

A She's going to put in the Phenergan first.

Q Okay.

A So she's—everybody has probably had their blood drawn at some time. Arm tied with elastic which has the venous blood not go up and shuts off the vein. So she would tie up Diana's arm in order to make the vein more prominent, she would probably try to not only see it, but you can tap on a vein. It's got a different feel than tissue, and locate the vein. She would wipe off the site with alcohol and get out this—this is called a butterfly infusion set. I don't know if we want to open that. We've got a different—another one here that's open. And these have a clear plastic tube connected. You can take off the device that closes that space, and then this would lock onto the syringe when ready.

Q Go ahead.

A So before—so she would take off this little cover and use these wings to hold the needle so that she could go into this vein and by—

[92] Q Excuse me.

A —by having the wings, I planned to keep this needle quite superficial, get under the skin—does feel a lot like skin—and then into the vein. You can then see some blood come back into this tube, sometimes it fills very much on its own, sometimes you have to draw back a little bit, and you see the blood come in. You can then make adjustment as to certainly whether that was dark, venous blood—you can see in this tube whether there were was blood that's dark as venous blood is or bright red as arterial blood should be. You might have to draw back a little to get the blood flow all the way back here. Arterial blood should be bright red and arterial blood sometimes will come back under more pressure. Venous blood should be darker. Sometimes you have to draw it and come back a certain distance—draw back to pull blood back into the catheter.

So this is an open system. She's in the vein, she's drawn her blood back, she takes off the tourniquet so that the blood can flow, the blood's moving through the vein, and she's got her three cc syringe with a blocking mechanism that locks on there, and then she slowly pushes that in. She's [93] got two cc's. She's got to take at least two minutes to put that in because the drug circular said you don't want to put more 25 milligrams a minute, and this is 25 milligrams in each of two separate cc's in this syringe.

So having done that, she can then unlock the syringe, put on her salt water so-to-speak, and wash that drug through. She's then got another syringe and she can put in her Demerol IV and she might begin to wash

that through, get the whole dose into the patient, not leaving some in the tube. Then she would normally put an alcohol—a cotton gauze over the site and pull out her IV. And hope it pulls out and stop and not bleed. I'm supposed to recap needles, but I don't think an eggplant will give me any trouble. So that's—that's the way it's done.

I would like to contrast that if I could to—

Q Could I ask you—the next question is there's another method of administering this or any other drug intravenously, right?

A There's also a third method I want to talk about quickly if I could. One could also take a drug, load it up into a syringe, push it into the [94] vein. And—as this one did—and then push the drug in. The drug circular makes note of the difficulty of the blood pushing back against the—the plunger. In the old days, which precedes most of us, there were glass syringes with glass apparatus which would move more easily and physicians were used to thinking if I got into an artery, it would push back and fill this thing on its own.

Q That's because the pressure in the artery will actually push it in?

A Push it open because these are not as slick, will not move as smoothly. That's not something to rely on. If you're going into the arm with this, you have not as much success as being superficial as you do here. The reason for being superficial is that veins are superficial and normally the arteries are deeper below what's called fascia, kind of tissue layer down in the muscle further away. So we elect not to use direct main linings so-to-speak with a syringe.

Q Is the butterfly system that you have described, do you use that in your practice or have you used this in your practice for all kinds of drugs?

[95] A Various drugs and for many years also it was used in the emergency room, no question about that, this same time period so it's—you call butterfly infusion sets.

Q What is the other method, which we will refer to as a free-flowing IV? Why don't we try and put these in the bag so that—

A Did the Tubex come back?

JUROR ONE: It's right here.

A So another way—a third way that one could use would be to introduce—probably set up hanging up on a hook—this little bag is very little, but you've seen IV bags that are bigger. They used to be bottles and this is this neutral saline which is not saltier or less salty than the body. So it neither adds water or pickles the tissue that it goes through. That would be set up with a—most people probably visited somebody in the hospital and seen this—an apparatus that would pierce the bag, the fluid would be run down, turn-off valve, run down and fill up this tube. This will be up in the air. This will be in it and you would have some dripping in here. The drops drop through and you can cont the drops and calculate the amount of the fluid that's going in. [96] This tube would be all filled up with this fluid. And these can be rigged to—could be rigged with butterflies, but would normally be hooked up with a device that is put into the patient like the needle like we spoke about, but then you can fill out this rigid obturator and that leaves this flexible catheter in the vein.

Q So there's a needle on here that you put into the vein, you take the needle out?

A And it leaves a sheath.

Q And this is just plastic. And that sheath is called a what? Catheter?

A A flexible catheter perhaps.

Q And where is that?

A That's in the vein and it's poking outside of the skin and has a little connector on the end so it can connect to this IV fluid. The fluid would then be running and one could inject their medication, Phenergan, Demerol, any other medication into a port in this IV and slowly put it in while the IV is running. The IV is dripping, the fluid is running through this at whatever rate and the medication can be introduced into the IV. You could either clamp off the IV, just pinch it and push sort of straight medicine with a little [97] dilution here or could have it run together, slowly push it in. This would afford a little dilution, but more affords the safety of not piercing back through the vein.

Q Why don't you explain in a little more detail, is this use of a free-flowing IV—put that back together before someone gets stuck, like me. Does this use of a free-flowing IV provide any additional margin of safety or assurance that what you're trying to put into a vein will go into a vein and not go into an artery or go into the tissue and then bathe the artery?

A I think that it would because if one were in an artery, this IV would not drip well and it might even have some slow flow of arterial blood back in because arterial pressure would push up against the gravity drip of the IV.

Q So if it's dropping into a vein, the pressure in the vein wouldn't stop the drip?

A You have to have untied your elastic, but it can drip at quite a fast rate.

Q And if it's in an artery—

A It would run against arterial cystolic pressure, 120, 140, and it would tend to run poorly. And you read the script of this happening [98] where blood comes back up into the IV set. I read an article where an anesthesiologist notices during surgery that whoops, we must be in an artery because there's blood coming back up into our IV infusion back and tubing.

Q What if you're inadvertently not in an artery but into the tissue outside the vein?

A Then you're going to—IV is going to run for awhile, but it's not in a conduit, it's in kind of a closed space. And once it's swelled up, it runs some cc's into tissue under your skin and amongst all the structures there, it's going to make it—we can call it a bubble, a fluid, but then it's going to be having a harder time to flow and it's not going to flow correctly.

Q If you were to set up this free-flowing IV and let it run for a couple or three minutes what measure of protection would you have against what happened in this case?

A You would have a lot more assurance that you were in the vein and not outside of the vein. And I think—I think it's clear that the injury could happen whether you were outside of the vein and in an artery or outside the vein around an artery.

[99] Q Okay. Why don't you take your seat. Have you reviewed the product information or insert that's Exhibit 1?

A Yes.

Q Okay.

A Not today, but previously.

Q Is the method—had you reviewed it before the incident?

A Absolutely.

Q And have you read it several times since?

A Absolutely.

Q Is the method that was used with the butterfly infusion set with that small butterfly consistent and appropriate under the instructions provided with a product by Wyeth?

A Yes.

Q Why?

A It's a functioning IV infusion set. The name of it is IV infusion set.

Q And is there anything else in the instructions with respect to dosage or needles that would further support a conclusion that it's consistent?

A Um, the product is said to be safe and [100] effective. I think it is in IV, and it's listed as appropriate to give it at 25 milligrams per minute, which can only be given 25 milligrams per minute, it shouldn't go faster. That has to be put in by IV push, slow IV push, as opposed to say being in a bag and dripped over a couple of hours. So that rate implies that or tells you that you can put in 25 milligrams every minute safely

into a vein. I have to say that in retrospect I think we're wiser about this and I must wonder why the 50 is labeled for IM only, the 50 milligram concentration per cc, but the 25 milligram is not labeled for IM only in that it turns out to be extremely caustic as it is.

Q What about the fact that the instructions appear to mention the use of—referred to plungers and rigid needles? Does that imply that you could give it IV push?

A It does, that you would be using it IV push. In the case of the plunger parts, I think we got around that by having the tube that could fill on its own. But by—certainly by talking plungers and rigid needles, that's the way you do it, to push it with the plunger.

Q Is the use of the butterfly infusion set, was it used in the—in April of 2000 [101] commonly to administer Phenergan?

A Yes.

Q Intravenously?

A Yes. We checked that. It was occurring at hospital in Bennington; certainly occurring in our patients seen at our emergency room. Several doctors in the hospital, when this came to their attention, came and told me that this scared the devil out of them because they—

MR. O'ROURKE: We object to that. That's certainly hearsay.

THE COURT: Yeah. I'll sustain the objection as to what people told you.

Q So the answer is yes, it was used at other facilities?

A Absolutely.

Q And why don't you always—you were aware of the risks of arterial—of this getting into an artery, right?

A Yes.

Q And they do talk about that?

A They talk about it in their package insert.

Q Yeah. Well, why then wouldn't you and others always use one of those free-flowing or [102] hanging IV systems?

A In retrospect I wish we had. At that time for this and a number of other drugs you're just going to be in the vein for two, three, five minutes and pull out the needle and be done. And so that the need for hanging a bag of IV fluid was less apparent. I also think that the idea of infiltrating was clearer to us. This is getting the material out of the vein. It might leak out of a hole in the vein or you might pierce the vein in the back and have some flow out around the vein and therefore bathe the artery. Concerned about local—in the anterior part of the arm tissue injury was clear to us. The idea that one would get into an artery seemed quite foreign to us and to everyone we spoke with because we were using the superficial approach with the butterfly needle.

As it turns out, and I'll tell you that none of—no one of us recognized this possibility—there is this aberrant artery business. It's not mentioned in the insert. They talk about arteries close by or something, but the aberrant artery—I think three percent on the side that Diana's injection was done on, maybe 14 percent on the opposite side of the arm, is just not something [103] that anybody is aware of. I did a literature search when we were trying to figure out what to do to help

Diana and I couldn't find any mention of any of this in a 25 year computer search.

We subsequently found articles by using the Dartmouth medical librarian to look further back than the computer could look for us. And we found some articles from 1968, '69, '70 talking about these injuries and aberrant arteries.

Q What is an aberrant artery? As it relates to this case?

A There's the usual anatomy where the veins are superficial, and the arteries are deeper, down in the muscle or below what's called fascia, kind of a glistening layer of something over the muscle, tissue—fibrous tissue. Aberrant arteries are arteries that are not in their usual location. So they can be both where you're not expecting them, and superficial, meaning closer to the skin, and therefore closer to the vein that you're targeting for your injection. We've learned that you don't have to be in the artery, you could soak the artery or surround the artery with fluid that got out of the vein by one way or another leaking out of the vein or if you counterpuncture **[104]** the vein all the way through, and that could injure the artery, probably soak into the artery. It could also injure the little nerves that travel with the artery that direct the artery to dilate or constrict. So it can damage the sympathetic nerve that run the dilatation or contraction of the artery. It can soak into the artery even if you didn't pierce the artery.

Q I'm going to get back to the insert in a minute, but can you tell us what happened to Diana's arm?

A Um, she came back in that afternoon with this discolored, painful—her arm was sort of bluish and

blanching and it was—the vessels were sometimes dilating and sometimes contracting. She had areas that would be bluish or white. Other times it would be rosy red and we—

Q Was there pain?

A Oh, there was pain. She ended up in this interval, the next two and a half or so weeks, taking quite a lot of narcotic pain relievers, both pills and patches that absorb through the skin and sometimes injections. So we spent about two and a half weeks trying to rescue her arm. And actually for a long time we thought we were succeeding. We

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[107] qualifications, and with a Doplar sound machine that uses a sound like radar, couldn't find any pulses below I think the point of splitting her brachial artery into her two forearm arteries. She also saw Dr. Michael Mason, who puts in a block to her arm to block the sympathetics hoping to dilate her vessels and to help her pain. And despite all of that, in our local hospital we were clearly failing, her limb was at risk.

We transferred her down by making arrangements by telephone to Dr. Jack Cronenwett down at Dartmouth-Hitchcock Medical Center and Dr. Curran did an immediate quick discharge note, some typed pages to send down with her, and she transferred down there.

Q Was the subsequent amputations that she had the direct result of the injection of Phenergan to her arm?

A Absolutely.

Q Do you know what the actual mechanism was that started this spasming and the subsequent gangrene?

A We know that the drug is extremely caustic. We know that if it it gets in the artery, it causes inflammation and spasming and eventually [108] an obliteration so they're gone to small vessels, capillaries and little arterioles, and therefore, one could have this bad looking, poor circulation in the fingers and still have pulses say at the wrist, for example. You apparently can get the same thing, from what we read, by extravating the fluid, having it go outside the vein and bathe the artery by injuring the artery. It may soak into the artery and go downstream or it may cause its trouble at the local.

She went down to Hanover. We didn't yet know all that was going to happen. And Dr. Curran had actually thought that maybe she had a local blockage of her artery in her arm from the vessel getting inflamed and narrowing down and getting a clot in it. So we thought she might be able to have the clot fished out and that section of artery repaired. I should say that we also during the course of this two and a half weeks got an ultrasound of her arm seeing if the vein had a blood clot in it because her arm was quite swollen. So in Hanover at Dartmouth-Hitchcock Medical Center, as I understand it, they—

Q I actually will talk to—I just wanted you to stop when your care stopped. When was the [109] transfer?

A We transferred her down to Jack Cronenwett at Dartmouth-Hitchcock.

Q What is the relationship between feeling pain and the damage that's done that causes this problem to start?

A I think in reading now that if you have severe pain down the limb, let's call it, that the damage is done at that point. No one we consulted in the course of this said look, you guys are not going to succeed at this. They all suggested what we were doing. But as we read now, and it may be that this was irreversible from that moment, that when the bad pain happens, if there's bad pain, the damage has been kicked off.

Q I think you started to answer this question a little earlier, but I wanted to ask you how this tragedy could have occured with the use of a butterfly infusion set? What were the mechanics—physiological mechanics that probably caused this to happen? You talked about the presence of aberrant arteries. Anything else?

A Well, I think that through inadvertance or an error this material got out of the vein either because the needle went through the vein and [110] was beyond it, counter puncture, make two holes and put it out in the tissue around the artery, or it leaked out of the vein through the hole that the needle was making, or it got actually into an artery. It might have been in the artery for a brief time and then when Jessica checked her position, it wasn't in the vein because the needle can make a little bit of motion. So then we could have had an aberrant artery near the vein that could have gotten bathed in or punctured and percolated with this medication. Or perhaps without even having an aberrant artery, the material could be in the arm, get around the artery enough to do this damage.

Q Is there any way to treat this effectively once it starts? Despite the reference, what does the literature say about that?

A We now know that one's quite apt to fail and there may be nothing that will succeed in this case. I

read some cases where similar treatments to what we did succeeded in saving somebody's limb. We don't know how much they got into their vein or around their vein. And I read some—a number of cases where everything failed.

Q Do you believe this product, Phenergan, [111] is safe with the instructions as they were written in Exhibit 1 in 2000?

A I do not.

Q Why not?

A I think that it—it does have some warnings, there is no question of that. But I think that the foreseeable accident or inadvertence is common enough that I think the drug should be labeled "Not for IV use." If it were going to be used IV, I think that it should say that it has to be in a running—established IV running at a certain rate. I'm not sure that I would buy the concept that if it were diluted, it would be safer, so I'm not thinking the IV would dilute it significantly, but it might better assure the IV route. But even then, you know, we're gaining 15 minutes of comfort. We're gaining some quicker relief. Seeing what happened and realizing it can happen in careful, experienced hands makes me think that this drug is inadequately warned, and frankly, we will not use it IV again diluted or in a running IV. We won't let that happen at the hospital to our patients and I don't think it should be used IV. I think it should be for IM and other uses, but not IV.

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[116] IV. It would have been IM. If we used it, Diana would not be in the position she's in with the loss of her arm and we would not be here.

Q If this said use a—if you're going to use it IV, use a free-flowing hanging IV system, do you have an opinion as to whether this tragedy would have happened?

A I think it would be extremely reduced in likelihood. I don't want to say it would be impossible, but the running IV would have given us more assurance of being in the vein.

Q I just have one more brief area of questions. I think we're going to hear from Mr. O'Rourke you wrote a letter to Diana at some point after this tragedy happened?

A I did.

Q And without getting into the particular details, what did you—what were you doing when you wrote this letter? Why did you write this letter?

A Diana and I had been friends for 20 plus years and I wanted to communicate to her my personal feeling of regret and remorse for what had happened. Frankly, it did me perhaps more good than her to get it off my chest.

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[159] to go home.

Q Doctor, does IV Demerol provide quicker relief than IM Demerol?

A Yes. Demerol IM can be erratically absorbed. Erratically—not just slower, it's less reliable in terms of the absorption curve so-to-speak.

Q All right. And how about Phenergan? Does IV Phenergan provide a quicker relief than IM?

A Yes, sir. It provides quicker relief probably by 15 or 20 minutes.

Q Okay. Doctor, we talked about—or you talked this morning about aberrant arteries?

A Yes, sir.

Q Under your direct examination. And Doctor, I'm going to show you what I've had marked as Defendant's E for identification, and it's an article from Moore & Daly on anatomy and ask you whether or not that document—and I have the book here—that's a portion of the article—whether that contains some information on aberrant arteries in the arm?

A I should tell you that this is the first day I've seen this sheet. It does say—and it's highlighted—that there's information—

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[164] Q Well, Doctor, so we won't have to ask you to come back here another time, let's assume that we're going to have evidence in this case, and evidence from the plaintiff herself, Diana Levine, that she yelled and she screamed that she was in pain; assume that's going to be in evidence, do you agree at that point that Jessica should have stopped injecting the medication?

A If she screamed out in pain?

Q Yes.

A That she had pain, I think that she should stop giving the medication. And I think from what we now know, that the damage to her arm would have then been already done.

Q All right. Now, you say you now know that, Doctor, do you know how much—how many cc's had

been injected into Diana's arm at the time that she screamed or yelled in pain?

A I don't know how much of that two cc's had gone in.

Q Have you had any scientific studies done to determine how much is needed into an artery before it's an irreversible situation?

A I read an article that said—in the peer-reviewed journal—that said that a woman in

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[183] A I found it in a like location, "For IM or IV injection."

Q Do you know of any reason or studies which support the use of this drug intramuscularly only for the 50, but for both ways for the 25?

A No, I have to say that—we've not been able to find anything. I don't know if any of your other witnesses have or not. I haven't been able to find any studies to say it should be safer at 25 per cc as opposed to 50 per cc. And I have to say that in retrospect, it's strange to me that one is precluded from IV use and the other is allowed for IV use.

Q Mr. O'Rourke asked you about the changes to the policies that are used at the emergency department up at the hospital. Now—after you wrote your letter saying that this was a dangerous drug. And could you tell us how they changed exactly? Do they—

A I think they changed before I wrote the letter. What I did is went and spoke to the E.R. director and I think before I wrote the letter to the medical staff as a whole they changed to require running IV and a ten to one dilution.

Q So what they did was they said they got [184] to use this system here?

A Yes.

Q Because it's safer?

A And dilute the drug.

Q Yeah, but this system because it's apparently safer?

A Safer in terms of route.

Q And in addition to that, they wanted or required that what comes in that Tubex be diluted ten to one or nine to one?

A Yes.

Q Knowing what you now know, do you think it's appropriate—it was appropriate for Diana to have received an intravenous butterfly injection of this drug? Phenergan?

A Absolutely not.

Q Why not?

A She should not have received it. She should not have received it because it's more unsafe than we knew and the enormous risk—even though the odds might be small in any one instance—is nowhere near offset by the small gain of 15 or 20 minutes less vomiting or nausea. I don't think the drug should be available IV and I wish that it hadn't been and then we wouldn't have used [185] it.

Q Now, when they asked you to read your letter of apology to Diana, the implication was that your testimony here today is somehow affected by the fact that

a claim was made against the Health Center and resolved. Is that the case?

A I'm not sure what the implications of those questions were. The case was made against the Health Center, resolved, and we had no deals. That I didn't even know this court case was going to come up. And this is nothing to do with that court case as far as I understand. We made—this was not a part of that process and I didn't know this was going to happen. And my being here today has nothing to do with that court case. We had some responsibility and we took it.

Also I don't know quite how the letter is supposed to reflect on my motives today. I back every word of that letter and I would say them with as much emphasis today as the day that I wrote it. But that does not make me come to court about this matter. I wanted to get the facts on the table about this drug. I don't think it should be available IV. I think that there were things we learned since this injury that made me understand

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[187] that says gee, why can't I give it IV? I do it all the time. We tell them absolutely you can't. I think it should be like Vistral and not be allowed to be used IV.

Q Other doctors at the Central Vermont Hospital use it IV?

A Yes, they do.

Q About the letter, I don't think anyone is intending to impugn your integrity, your abilities as a doctor, your abilities as a physician, your treatment of Diana, but the letter indicates you said that you accept responsibility for what happened to Diana, isn't that so?

A Yes, it does.

Q And what responsibility do you accept? I mean what did you do wrong?

A We chose this drug. We administered it as directed in the package insert. And that's part of our responsibility. We had to make this choice. It's our position there is a drug company, there is a patient, we're in between. We're supposed to have a cooperative, collegial, mutually helpful to our patients relationship. And in this instance we chose and used that drug in good conscience. I think that Jessica appropriately used it, although [188] I now knowing what I know now, I think we shouldn't have used it. Diana shouldn't have gotten it, and the—I think that in this case the trust relationship between the drug company and myself as a medical practitioner broke down. We should have had more warnings about this. If cases were being reported to Wyeth, we should have had the representatives who come and sell us drugs should have come and told us about this problem. It shouldn't have been submerged in the literature for 30 years. And the instructions and warnings and so forth as they're printed I think are inadequate, insufficient. I don't think the drug should be used IV.

So I'm responsible for having used what I believe now is a product that shouldn't have been available to me to use. I'm also responsible for any error that Jessica made, whether it's inadvertance or accident. I'm responsible to the extent if we could have found any solution for Diana's injury, I'm responsible for our not having—maybe there was no solution, but we did our best to find it. So I wouldn't change a jot, as I said, of that letter, but that doesn't mean that there's no responsibility for Wyeth. There is some

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[Testimony of Dr. Harold David Green]

[194] A Yes, I am.

Q Okay. What is the difference between the free-flowing system and the butterfly system from your perspective in terms of safety?

A The free-flowing system is where you will hang an IV bag full of solution usually saltwater or dextrose, sugar water, and that is dripped into usually a catheter that we put into a vein rather than a rigid needle. So the catheter is introduced with a needle and—with a needle poke—but then over the needle is slid a soft rubber catheter, or some other polymer other than rubber, and the rubber catheter stays in the vein. Being soft and plastic, it doesn't penetrate the vein anymore. Once it's introduced, it stays there. And then that's hooked up to the intravenous tubing to an IV and the fluid is dripped through that.

Q This is in evidence. The jury took a look at this. I can't take it apart. You do it. Okay. Now the jury saw that this morning the catheter to which your referring.

A Yes.

Q And the needle comes off?

A Right. So there is a needle in the [195] center with a soft catheter on the outside. Once you penetrate the vein, then the catheter is slid into the vein and then this needle is hooked up to the intravenous tubing which is hooked up to an IV bag of solution.

Q Does this system of using a free-flowing IV protect the patients from either an arterial injection or the infiltration of the drug outside the vein and into the tissue?

A Yes. This technique almost precludes an intra-arterial injection if the IV is running. If it's adequately running. It can still extravasate sometimes, but usually when it extravasates it occurs immediately.

Q What is extravasate?

A Well, when this needle enters a vein and the catheter is then slipped into the vein and the needle is pulled out, then you start running the solution in. If the needle went through the vein in two places, or if it went —just sort of hit the vein and then came back out and the catheter actually sorts of goes through the vein or out the back wall, now the catheter is not totally in the vein, as you inject—as the infusion, the fluid drips in, it will extravasate which means that it **[196]** will end up outside of the vein so that happens almost immediately. As soon as the IV is started, you see it dripping and if it is not in a vein, it has either a lot of resistance so that the IV will not run or the nurse or whoever is doing it will notice a little bit of pain oftentimes and some swelling and then as the swelling gets larger at some point the intravenous will stop.

So at the very beginning of the intravenous first setup, this has a risk of extravasation, that is fluid going outside the vein. But once it's running, once the catheter is in a vein, this catheter is longer than the butterfly, it's soft, it isn't—even if the patient moves, it isn't going to puncture the vein anymore. There's no sharp object in there. So it's very rare for these to extravasate after everything has been established when it's running.

In addition, because the intravenous—you can calculate sort of simple physics—that the blood pressure in our arteries, as you all know, is typically 120 over 80 is the typical blood pressure. That's a pretty high blood

pressure. That's enough to push a column of water up about five or six feet. So if you put a needle in an [197] artery, and you hooked it up to water, it would push that water five or six feet up. And that's where the IV is hung. It's hung, you know, about four feet up or even less, three and four feet. So if there's—if it's in an artery, the blood from the artery will go up into the catheter and into the IV rather than the IV fluid traveling into the artery.

So a running intravenous, once it's established, is a far safer means of administering any medication to prevent extravasation and to prevent arterial injury or arterial injection.

Q So if you let that saline flow for a few minutes, you would be pretty well assured that it was in the right place?

A Yes.

Q Before you put the medicine in?

A Correct.

Q How often do you use the direct infusion or the free-flowing system, not with Phenergan, but generally?

A Most of the time we're administering fluids to patients and so when people are vomiting, they come to the emergency room, they'll be dehydrated as well, so in that case we want to give [198] them the fluid so we establish the intravenous, and I would say that's the majority of cases. We might inject some medication through the free-flowing intravenous solution as well as giving them the solution itself. So the majority of the time we're using a free-flowing hanging IV system.

Q But you also have used the other?

A Yes.

Q And you're a pharmacist, right?

A Yes.

Q Most of us know what a pharmacist is, but how does it relate to what you're here to talk about?

A Well, as a pharmacist, I was trained to understand pharmacology of drugs. That is how they work and also the process by which drugs are approved by the government for use in the country and the properties that are involved in that processes. With my pharmacy degree I've continued, as I said, to maintain my registration in pharmacy and at the previous hospital that I was at, as well as at Tufts New England Medical Center, I'm the chairman of the pharmacy committee.

Q What is the pharmacy committee's role at this—at your hospital?

* * *

[208] guess briefly is better than generally—what your understanding of how the Phenergan was administered to Diana Levine in this case. We've heard testimony a few minutes ago about that so just tell us what you understand.

A My understanding is that the nurse—one of the nurses at the Health Center took two 25 milligrams per ml, and cc is the same, Tubex syringes, took the drug out of them, and injected them into the barrel of a standard three cc syringe.

Q Is there one in there? Three cc syringe in there?

A Yes. And then while she was doing that, or about that time Jessica Fisch had inserted the butterfly

into this part of the arm, the antecubital space, into a vein. And got back flow, got blood return. And then Jessica took the syringe with the 50 milligrams, now two cc's of Phenergan and hooked it up to the tubing of the butterfly and injected that over about two minutes.

Q And how—how would you determine that this system is functioning properly? You're using that infusion set. You've explained how you would determine if it were a free-flowing system, but how [209] do you determine that that system is functioning properly before you put in the medicine?

A Well, it's a little bit harder to be as certain with this system. What one does is when you put the butterfly in and you get return of blood, if youo're in an artery, the blood shoots out and is bright red. You're in a vein, the blood—you get blood return, and if you're not in anything, you don't get any blood or just a quick flash and that's all. So to determine if it's in a vein where it should be, you get back sort of darker red blood not under high pressure.

Q Is it possible to be fooled with this system?

A Yes.

Q How's that happen?

A Well, first of all, because you're using a needle and the needle stays—well, a assuming put in the vein to begin with, if you're in the vein, the patient moves over a couple of minutes, we move a little bit and it may puncture the back side of the vein. And if there is an artery that's very superficial, very close to the surface, you can puncture an artery or it can just extravasate. It can just go outside of the vein and then bathe [210] an artery that's nearby. So the fact that you have a sharp object, a sharp, rigid needle in the vein is a prob-

lem and then you don't have the safety features of a running intravenous that would stop if you extravasated and you have a catheter instead of a sharp needle in a vein. So it's just generally not as safe. We frankly generally don't like to administer medication this way. If the patient needs an IV, we would much rather have an IV running, just a more secure way.

THE COURT: Mr. Rubin, this is probably a good time to take ten minutes.

MR. RUBIN: Yes, sir.

THE COURT: Let's do it. So about quarter after we'll all get back together. Everybody can stretch.

(Court recessed from 3:03 p.m. to 3:13 p.m.)

MR. RUBIN: I'm sorry, your Honor. I didn't realize—

THE COURT: Not a bit, no, no, no. It's fine.

Q (By Mr. Rubin) What is your understanding, Dr. Green, of what actually happened to caustic the injury in this case?

A My understanding is that when the [211] Phenergan was injected, some of it or perhaps all of it escaped from the vein. It either went through the other side and it either bathed an artery, that is it extravasated out of the vein, or it actually entered an artery directly. I don't think anyone can tell. This type of thing has been reported in either case where there's extravasation of the Phenergan apparently close to an artery or direct injection into an artery.

Q And could this have been caused by the Demerol?

A No.

Q Why not?

A Demerol is frequently given with Phenergan and as a pain reliever, however, it's actually been studied with Demerol. There was a study done in I believe it was in the late '60s where Demerol was injected along with other substances into the veins of animals and it was determined that Demerol doesn't caustic that effect that other drugs like Vistral can caustic this effect and Phenergan.

Q And what is the mechanism by which once it's in the artery the arm goes into gspasming and ultimately the tissue dies?

[212] A The—I think there's not a complete understanding of how this happened. However Phenergan in a general sense and some other drugs like Vistral are irritants to the artery. They somehow damage the internal lining of the arteries especially the tiny arteries. As the artery goes down the extremity, they get—they branch out and they get smaller and smaller and apparently these very small arteries become damaged. There's also some degree of gspasming that the artery goes in as an irritation just by being irritated or by damaging the nerves around the artery, that the artery has little muscles in its walls and it constricts, so you get a combination of constriction of the blood vessel, the larger blood vessel, and then damage to the blood vessels—the smaller blood vessels further downstream. And that damage actually then continues to produce problems because the blood gets stagnant again. It doesn't flow through the arteries so the blood starts to clot. So it's a combination of gspasming, inflammation and clotting. And then the very tiny blood vessel actually starts to leak fluid and fluid accumulates around the arteries, and it's a combination of a number of

things which is probably [213] why there isn't any good, simple, straightforward treatments, even though many different things have been tried such as anticoagulants, nerve blocks to allow the blood vessels to dilate and medications for dilation, and even drugs that break up clots. And there isn't anything that clearly works probably because it's a multitude of different things that are happening to the arteries at the same time.

Q Is it foreseeable that the use of a butterfly infusion set like the one used here will result in some cases this will happen?

A Yes.

Q And why is that?

A Um, directly injecting a medication is not a process that's a hundred percent foolproof no matter how much experience a clinician has, no matter how much care they take, there will be sometime when they will be near an artery and not be aware of it or extravasate the medication. That's just the nature of direct intravenous injection. It's not a foolproof process regardless of the amount of care that's taken by the clinician. So this is foreseeable, that if it's permitted, if it's recommended that direct arterial [214] injection—I'm sorry—direct injection of medication into a vein or attempted into a vein is just foreseeable that at some point in time you do this enough times and the fluid medication will either extravasate or be inadvertantly be put into an artery.

Q Is there anything in the literature or other information that you've reviewed to show that that reveals that this has happened before other than just that it's likely to happen as you described it?

A Yes.

MR. HOFFMAN: Pursuant to what we discussed in chambers, I have an objection to this evidence.

THE COURT: Understand. Overruled and you may continue.

A Yes. There's information in the literature and there are reports of this happening with 25 milligrams of Phenergan or less. It's happened with 50 as well. All by direct injection and generally by nobody trying to get into a vein, but, you know, most cases—

Q Nobody trying to get into an artery you mean?

* * *

[216] the—in those reports as it relates to the kind of event that occurred in an administration similar to the one that happened in this case with a direct infusion?

A Yes. The reports indicated, along with the files from Wyeth, plus what's in the literature, that since the late 1960s there have been at least 20 cases where Phenergan has caused an amputation. There have been many more cases where the person's arm or hand or finger has turned blue for a while and luckily no amputation occured.

Q We're talking only about direct injection here, not any other method of injection?

A That's correct.

Q Okay. Is there anything in the actual product information itself that says that this can happen?

A Yes.

Q And what's that?

A Under the section that says Inadvertent Intra-arterial Injection. Would you like me to read part of it?

Q No, I think Mr. O'Rourke read that, but it's in the literature itself that there are reports to that effect?

[217] A Yes.

Q You may have already just answered this question, but is it foreseeable that this will happen with the butterfly as opposed to the free-flowing IV? I think you may have answered that question.

A Yes. It's theoretically possible to happen with the free-flowing IV, but it's harder to do and it's almost expected that at some point in time it will definitely happen with the butterfly setup.

Q Okay. Is there anything in the literature about the presence of abberant arteries?

A Yes.

Q That's relevant to your opinion?

A Yes.

Q What is that?

A The literature says that there are blood vessels, arteries in the upper extremity that are aberrant. That is they either don't exist in the majority of people or they exist but they take a different course. And that's important because the artery, the main artery in this part of the arm, the antecubital fossa that we call it area, that artery is called the brachial artery and it is [218] deep, very deep. And sometimes we actually do try to penetrate that and we usually need a rather long needle to go straight in. That's the usual course of that artery. But sometimes the artery actually branches up

higher and takes two branches that come down, become superficial. So they're right underneath the veins or at the same level as the veins. So it can be abberant in the way the way the artery branches and its location or it can be just a separate branch that most people don't have that shows up. The incidence of the artery brancing early is about 13 percent of people and the extra artery, if you will, that's not there in most people is about three percent. So it happens a moderate number of times that that type of thing can occur.

Q Is it foreseeable that this will happen in a number of cases by a clinician making a mistake somehow?

A Well, it will occur even with a careful clinician because they will just be unable to determine whether their person has an abberant artery or whether they've actually penetrated through the vein and entered an artery with a butterfly set. You just can't tell at times.

* * *

[225] Q Now, Tubex syringe was not used in this case, a different kind of syringe was used. Does your opinion still stand?

A Yes.

Q Why?

A Again, it's the direct injection that's more important than whether a Tubex is used or not. Because by directly injecting medication into a vein or what you hope is a vein, someday someone will be outside the vein and they will not know it. They will not be aware or in the sense that's detectable, it's an error, a problem, and it will ust occur as certainly some accidents occur such as being struck by lightning. It will happen someday to somebody. And it's foreseeable.

Q Well, a little more foreseeable than lightning, right?

A Yes.

MR. HOFFMAN: Your Honor, I object. Side bar comment from counsel. It's argumentative.

Q Is it more foreseeable than a lightning strike?

THE COURT: All right, all right, I think we get the point.

MR. RUBIN: I'll withdraw the question.

* * *

[230] MR. RUBIN: We won't use that document.

Q Do you believe the warnings and instructions contained in the Wyeth product information were adequate to make the product safe?

A I do not.

Q Why not?

A I think the warnings and statements in the package insert by Wyeth, first of all, say that given intravenous Phenergan is well-tolerated, but not with some risk. I think the cases that I've seen and what happened here are certainly indications of more than some risk. And that that statement implies to the clinician that go ahead and use it, it's a pretty safe product, and go ahead and give it by direct intravenous injection. But they also say that intra-arterial injection, even though it isn't meant to be an intra-arterial injection, has happened from time to time. But it's still okay to use the drug by direct injection when it is clear that most clincians and the manufacturer know that there are safer ways of administering this drug than by direct injection such as by using a free-flowing IV.

In addition, the manufacturer has implied that the 50 milligram concentration is the unsafe [231] concentration to be injected intravenously, whereas the 25 milligram is safer. There is no information that backs that up. Certainly dilution may have some effect, that is the less concentrated solution might in fact be less dangerous, but there are cases of this happening with 25 milligrams or less and there's no study that's been done to support the 25 milligram per ml injection over one minute being safe.

Q Do you believe the language in the warning that's says that the veins and arteries are close to each other in the area where you're likely to inject it is sufficient to warn of probability or possibility of abberant arteries?

A No, I don't think that's sufficient. I teach medical students and, you know, we have anatomy usually in our first year of medical school and unless we become surgeons and become intimately involved with specific areas of anatomy, this isn't something that most clinicians would be aware of who use this type of a product. Give it to an obstetrician, he's not going to know or remember much about arm anatomy. Even if he learned about abberant arteries, he won't know very much. But an abberant artery is much different than an artery in [232] a vein being in proxiimity—I mean they were in proximity, but they're abberant. But warning a clincian that arteries are different in different people and you may not be aware of the fact that there's an artery right next to that vein that usually isn't there. Because what we do learn, most medical students and residents, learn how to do a blood gas, how to take blood from an artery at this point. And it's hard and it's deep and you can't—it's hard to feel. So that's what our experience is and I think the manufacturer should have clearly said

that abberant arteries can be present and you can't tell and you don't know which patient they're going to be, who you're going to find them in.

Q Now, that's the kind of alerting you of what can happen, but what about the instructions themselves? Do you think those are adequate on how to do it or how you can do it?

A Are you referring to the—

Q IV infusion set that's known to be functioning properly?

A Right. Well, that—that's inadequate in that I really feel that this drug is probably not safe for intravenous injection at all. There [233] isn't any need to use this drug intravenously and, as we know, Vistral, a product made by another drug company called Pfizer, the drug company voluntarily decided back in about 1970 not to allow Vistral to be used intravenously because of problems such as this, where people have got gangrene and amputations, and the manufacturer decided it just isn't a drug that's so important to be given intravenously that they decided in the package insert to say IM use only, no intravenous use.

So in the first sense, I believe this drug is not—there is no desperate need to recommend its use intravenously. And if it's used intravenously, then the manufacturer I think is obligated to tell the clinician what is the absolute safest way that this could be given intravenously? And that would be through a free-flowing IV, not through a functioning infusion set.

MR. HOFFMAN: Your Honor, pursuant to our discussion in chambers earlier, I have an objection to the evidence on Vistral.

THE COURT: Okay. I'll overrule the objection. But appreciate you bringing it up.

MR. HOFFMAN: Thank you, your Honor.

[234] Q Wyeth has said that there was a complaint of pain by Diana Levine when the IV was started and the medication went in. Do you have any opinion with respect to the fact that the company warns that you should stop when there's pain as to the outcome in this case?

A Yes, I do.

Q What is it?

A In my opinion once the patient experiences pain, that is an indication that the drug has damaged the artery. Arteries are not usually painful unless they've been injured. So presence of pain shows that a problem has occured. And there have been cases where the patient has complained of pain and injection immediately stopped and they've gone on to have necrosis and amputation. So I think there's nothing in the literature that says that once the pain occurs, once the probable intra-arterial or peri-arterial injection occurs, that there's anything that will prevent it from getting worse.

Q And what should have been in the instructions or the product information that would have prevented this from happening?

A Well, the best thing to have been in the [235] instructions was do not use our product intravenously. It should be for IM use only. That's the best thing. The next best thing would be to talk about aberrant arteries, to talk about using the medication only through a running IV, and it would have been best if the manufacturer had done studies to find a concentration that was

safe. So if they said take 25 milligrams and diluting it ten-fold or twenty-fold or fifty-fold, that when we do that in animals, we have don't see any problems and that would have been a very safe and easy thing for them to do. That they could have—if they found the concentration that was safe to have put in the literature.

MR. RUBIN: Thank you. Your witness.

Cross-Examination by Mr. Hoffman

Q Good afternoon, Dr. Green. I'm William Hoffman and we didn't meet until just on the break?

A Hello.

Q Is that correct?

A That's correct.

Q Dr. Green, in the United States who has the responsibility for deciding whether a drug should be available for marketing?

A The manufacturer of the drug with the [236] approval of the Food and Drug Administration.

Q Okay. And is it true that the FDA assesses the benefits and risks of a drug before it allows that drug on the market?

A It does today, but it didn't back in 1950.

Q Your testimony is that the United States Food and Drug Administration did not review the effectiveness and safety of Phenergan and approve it for marketing?

A The—now, I'm not a lawyer so I don't—I'm not—but this is my understanding, that the Food and Drug Administration, the Pure Food and Drug Act ini-

tially allowed the FDA to determine that drugs were safe. And that they were labeled properly that if the package said it had 25 milligrams of Phenergan, it had 25 milligrams of Phenergan, give or take a little, but it wasn't until much later that the Food and Drug Administration in a subsequent amendment to that Act was given the authority to determine that a drug was effective.

Q Do you know whether—do you know what a New Drug Application is?

A Yes.

* * *

[240] issue here is appropriate to use?

A Um, I've seen documents from the FDA to Wyeth and from Wyeth to the FDA stating that Wyeth's best thinking was that this medication, Phenergan Injection should only be administered through a running intravenous. And that the letters back and forth that I saw indicated that the FDA was in agreement with that. However, the final letter from FDA to Wyeth for some inexplicable reason says forget what we told you before, and we don't think—and just keep—keep the labeling the same.

Q So the answer to my question is yes, the FDA approved the form of the labeling that we've been talking about today, correct?

A I think somebody at the FDA made an administrative error and approved it, yes.

Q Did you talk to anybody at the FDA about this?

A No, but I read the several letters back and forth between Wyeth and the FDA.

Q Okay, and you read the label—the letter that said this labeling that you're using is appropriate, you may continue to use it? Correct?

A Um, words to that effect, yes.

[241] Q Okay. You've never worked for the FDA?

A That's correct.

Q You never consulted with them?

A About this case?

Q About this case.

A No, I just asked for reports that they had.

Q You've never worked in the development of a drug, have you?

A No, I haven't.

Q Never worked for a pharmaceutical company on labeling for a product?

A No, I haven't.

Q You're not an expert on FDA regulations, correct?

A That's correct.

Q You've testified that there should be no ability for physicians to use Phenergan intravenously in the United States, correct?

A Um, well, what I would say is that the manufacturer and the labeling should say for intramuscular use only.

Q Which would have the effect that doctors, unless they wanted to ignore the labeling, not to use it intravenously?

* * *

[246] Q But for the patients that you prescribed the medication, you believed that the benefits of using the therapy outweighed that risk?

A Yes, I did.

Q Now, let's talk about efficacy for a minute. You would agree with me that there are situations in which a patient is vomiting so profusely, so continuously that they need immediate relief for their health?

A I'm not sure.

Q You're not sure?

A I'm not sure I've ever come across a patient vomiting so much that they needed relief of the vomiting. They may need intravenous fluids rapidly, but relief of the vomiting is secondary.

Q We'll turn—come back to that. You agree that Phenergan IV is effective in controlling nausea?

A Yes.

Q And you agree or are you aware that there are emergency care textbooks—that's your field, right, emergency medicine?

A Yes.

Q That there are emergency care textbooks that recommend the use of Phenergan in situations

* * *

[249] help myself.

THE COURT: We'll continue.

Q Oncology, it's used in cancer patients quite frequently, isn't it, for nausea?

A It can be. I'm not sure how frequent.

Q Okay. The labeling indicates it can be used in amelioration of allergic reactions to blood or plasma. Are you aware of that use?

A Yes, but I don't—I've never used it for that.

Q Okay. How about for anaphylaxis as an adjunct to epinepherine and other standard measures be used in that situation, right?

A Well, that's—think—that's not a good use given that it even says in the package insert that the use of epinepherine with this drug is a problem. So this contradicts itself within the same package insert.

Q Okay, the only point I'm trying to make is there are several uses of this drug. It's not just nausea, correct?

A In the year 2000 there's—I think probably the only use of this medication would be nausea.

Q All right. So you think the FDA got it [250] wrong here, too, in approving a labeling that it has nine separate indications?

A I think that this drug is so old that many of these indications date back many, many years, and we no longer do these things. We no longer use this drug—given that many other drugs have come along—this is no longer a preferred drug for any of these indications. Not that it was never safe or useful.

Q Okay. I think we're in agreement. Of these nine indications how many of them does the package insert state should be given intravenously?

A Well, it says during surgery—special surgical situations it mentions intravenous use.

Q And I think actually in fairness, although it's not in the Indication section, I think you're flipping back later on in the Dosage and Administration section. There is a statement also I think about post-surgical—for post-surgical nausea and vomiting?

A Yes. It says for nausea and vomiting it may be given intra-muscular or intravenously and then pre-op and post-op.

Q Pre-op and post-op?

A It doesn't specify.

[251] Q Okay. Those operative situations would be situations generally when a hanging IV bag would be either set up or quite readily available, would you agree with that?

A I'm sorry, which situation?

Q Pre-op, post-op.

A There's probably one post-op. Pre-op there may be just what's called a saline lock.

Q Other medications that could have been used the day Ms. Levine came to the clinic, we talked about compazine. That has risks associated with it, doesn't it?

A Well, compazine has some of the same risks as Phenergan. It has no more risk and it has no risk of intra-arterial injury. So in other words, it has less risk than Phenergan.

Q Right, but it does have risks. You agree all medications have risks, correct?

A Yes.

Q I think you even testified that placebos have risks?

A Right.

Q So compazine has risk, right?

A Yes.

Q And actually Ms. Levine, I think Mr.

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[267] said she was feeling pain or yelled that she was in pain?

A I know there was enough injected to caustic pain. I don't know the quantity.

Q It could have been one or two drops, right?

A And one or two drops have been reported to this caustic this problem.

Q There was an article in the literature that said there were one or two drops that caused the problem?

A There was what was described as two minims, which is an old-fashioned Latin term for drops, of diluted five cc solution, so it was even diluted and somebody lost a finger.

Q Okay. Dr. Matthew said that he was only able to find one case report in which 10 milligrams out of 25 had been injected.

MR. RUBIN: Objection.

Q Are you aware of that case report?

THE COURT: Hang on just a second.

MR. RUBIN: It's inappropriate for him to characterize. You can ask him in the form of a hypothetical, but for him to just say what someone—some other witness said and then ask him to

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[270] A No.

Q Okay. The labeling, the Warning section also instructs physicians to stop an injection if the patient complains about pain, correct?

A It does.

Q Okay, and that's an instruction to physicians and others who are administering this medication, correct? Stop.

A Yes.

Q Now, you gave some testimony about the phrase in the label that the physician should use an infusion—IV infusion set that is functioning satisfactorily, correct?

A Yes.

Q That can include a hanging IV bag. Correct?

A That could include that, yes.

Q And you've testified that it could include a butterfly set, correct?

A Yes.

Q Do you know how many times Phenergan has been given IV injection in the United States since it's been on the market?

A No.

Q Do you know how many times it's been

* * *

[272] THE COURT: I'll allow it for cross-examination.

A I believe that Ms. Fisch used the typical extreme care that clinicians use when they inject medications directly.

Q Okay. I want you to just assume for the purposes of my question that there will be testimony that Ms. Levine, when the injection began, yelled or screamed in pain. Was it extreme caution not to stop the injection at that point?

A If in fact Ms. Levine had screamed in pain, it would have been desirable to stop the infusion to see what was happening.

Q Okay. You mentioned the product Vistral. Vistral is a different drug than Phenergan, correct?

A Yes.

Q Different chemical makeup?

A Yes.

Q Different mechanism of action?

A Probably not.

Q Well, it doesn't have the nine indications that Phenergan has, does it?

A But it's an antihistamine, antinausea medication.

* * *

MARCH 9, 2004

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[Testimony of Daniel J. O'Brien]

[10] care provider.

In the case of perhaps a serious adverse event being discovered about their drug, the manufacturer will write to say their obstetrician's using this drug. And there's something that the drug company—serious side effect or something that's been uncovered that they

will send out what's called a "Dear Doctor" letter or "Dear Pharmacist" letter and giving this updated information.

Q Now, does the drug company have the right or the ability to change a label without FDA approval?

A Under certain circumstances they can change the label without prior approval of the FDA.

Q Right.

A Usually if you want to change a label, which is—I'm talking about the physician's package insert now, for a new indication, say you want to treat another disease with it, you can't just do that. You have to submit data to the FDA for a new indication and get their prior approval. However, if there's a—you come across a serious side effect from your drug, you can change your label. There's a provision in the FDA regulations

* * *

[14] something about—that perhaps an instruction of how to administer a drug was not clear or not detailed enough or maybe a wrong—I hate to use the word wrong—but a better method might be used to administer the drug. So the manufacturer can just—can go ahead and instruct changes insert and publish that insert and distribute that insert with his strengthened or additional statements about—or instructions about the dosage or administration.

Q So if the company decided that it was unsafe to use a butterfly to administer a drug, they could change that without permission?

A Yes.

Q Advance permission?

A If that's what they felt, yes.

Q Number four, they can actually—it says, "To delete unsupported indications for use." Do you see that?

A Yes.

Q Would that include if it wasn't supported to use this drug intraveneously they could just pull this out?

A Yes.

Q Thank you. I don't have a slide for

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[18] some was provided to me. Well, the regulations, of course I looked at those. Adverse Event Reports.

Q And what was—what—what was the question about the product?

A Well, is there any reason to believe that the labeling of this drug was deficient in some way? Any way?

Q Okay. And what product were you looking at?

A Phenergan.

Q A Tubex injection product?

A It's an injectable product.

Q Do you know generally the method that was used to administer the product to Diana Levine?

A As I understand, a butterfly was used and a regular push syringe.

Q As opposed to a free-flowing IV?

A Correct.

Q Are you generally familiar with the difference between those two techniques?

A Generally, yes.

Q Was the technique used by Jessica Fisch, which the jury has seen, consistent with the instructions that were in the product information?

A It would be reasonably included, yes.

[19] Q Why is that?

A It was functioning properly.

Q So was an IV push system consistent with a system here?

A Yes. With what was used, yeah.

Q What is your understanding of what happened in this case? What happened?

A Well, I understand that she suffered tissue damage and resulting gangrene and which required an amputation.

Q And what was the product that caused that? Was it Phenergan?

A Phenergan, yes.

Q What about any other cause product, Demerol?

A No, not that I know of.

Q There was some indication that there may have been pain when this drug was administered; are you aware of that?

A I've heard that, yes.

Q And what is the relationship as a pharmacologist between the administration of this drug and the pain?

MR. HOFFMAN: Your Honor, I have an objection. If this is a nondesignated opinion,

* * *

[21] MR. RUBIN: He's not going to say that it was too late; he's going to testify that the causticity of the drug is consistent with pain. The pain is—

THE COURT: All right. That's not in dispute anyway.

MR. HOFFMAN: If that's all he's going to say, then I have no objection. I thought this was leading up to—

THE COURT: Fair enough.

(Open Court)

THE COURT: So I'll overrule the objection.

MR. HOFFMAN: I'll withdraw it on the basis of what Richard said.

THE COURT: Fair enough. That's fine.

Q (By Mr. Rubin) When there is pain when this drug hits tissue, what's actually happening?

A Well, there's irritation first and then if it's strong enough of an effect, you have cell death, actual cell death.

Q Is that what's causing the pain?

A The—first of all, the irritation would affect the nerve endings and right away cause pain. If it's severe enough, there would be—[22] cell death would occur. Just like we burn ourselves with a match or something, there are degrees of being burned.

Q Can you comment generally on the causicity or corrosive nature of this drug and the liquid that it comes in?

A Well, it's formulated to a pH, that is acidity or basis towards the acid side, and it contains phenol, which it can be a serious chemical irritant to the skin or even corrosive to the skin. There are numerous instances where the corrosive nature of this drug—by the drug, I mean the whole injectablbe formulation—causes cell death if—for instance, they say—the manufacturer states "Do not administer subcutaneously."

Q What's subcutaneously?

A Under the skin.

Q I need to take just a second and distinguish that between intra-arterially and intravenously.

A Well, that would be administered just under the skin.

Q Are some drugs—

A Not attempting to go into a vein or anything like that.

* * *

[24] A Yes.

Q And that's caused by—you believe—the corrosive nature of the drug?

A I believe so.

Q Do you believe it's a foreseeable risk that some significant danger or harm would happen if this drug is used with an IV butterfly push system?

A Well, certainly seems entirely possible—

Q Why is that?

A The manufacturer has stated not to administer this in a dosage more than 25 milligrams—dosage strength of more than 25 milligrams. They state that

their 50 milligram dosage form is not to be administered IV, strictly intramuscular use. They say to administer it very slowly over a minute or two minutes. This is an attempt to dilute what's going into the vein, go in slowly. It's like leaking, dripping something into a stream. You want to have it diluted, so that's an attempt to dilute it. The best dilution of all, although we have no real specific instructions from the manufacturer on how much dilution can put to the drug, it can administered—

* * *

[26] started to talk about the 50 milligram dosage is for intramuscular use, 25 apparently is for both ways. Go ahead with your answer about why this is not safe.

A Well, it's already happened administering the 25 milligram dosage form. When extravasated into the surrounding tissue it has caused damage, cell damage.

Q So therefore you wouldn't want to do that either way?

A No.

Q Are there any particular problems that can arise using the butterfly needle as opposed to a free-flowing IV?

A Well, you have the lack of a very large dilution for one thing. The needle could move and it could go through the vein or it could actually go into an artery and then you don't have the warning of feeling or having the back pressure from the—if you hit—go into an artery, you don't have enough force to push the plunger back.

Q Which means what?

A Which would mean help guide whether it's in an artery or not.

Q Was there anything in the literature

* * *

[28] Q What is Vistral?

A Hydroxazine and it had antihistaminic properties like promethazine for Phenergan.

Q What was it used for?

A The same sorts of thing Phenergan was used for.

Q Nausea?

A Nausea, hm-hmm.

Q And is that used for intravenous use anymore?

A No, it's been withdrawn. The manufacturer withdrew it.

Q It's still available though for intramuscular use, do you know?

A That I can't say for sure.

Q Is there any indication that this event was preventable? Well, let me ask a different question. Would you have an opinion as to the adequacy of the instructions and warnings contained in the product insert?

A Well, I—I thought it should state a free-flowing IV rather than just a functioning IV, which would allow use of the butterfly then—and I didn't think the butterfly should be used.

Q What about using it IV at all?

* * *

[35] A It used to be, yes.

Q Okay. And you even found out through your search that there were particularly abberant arteries in the arm, correct?

A In the antecubital fossa, yes.

Q Do you agree that the FDA knew about the risks associated with this product that we've been talking about? Yes?

A We certainly assume that, yes.

Q Well, you know?

A And they have discussed that.

Q This they have discussed that?

A In correspondence back and forth.

Q You've seen correspondence in which this risk that we're talking about has been discussed?

A Hm-hmm.

Q And you agreed that FDA receives adverse event reports from doctors as well as from the company, correct?

A Primarily from the company.

Q And the adverse event reports that we've been talking about that were in Wyeth's files you know were sent to the FDA?

A Yes, I asume that. I feel that, yes.

Q Did you review the New Drug Application?

* * *

[45] That's fine. Last time you published a scientific article was when you were a graduate school, correct?

A That's correct.

Q And you've agreed—you agree with me that one thing you haven't done over your career is offered your services as expert in any field of medicine?

A Oh no.

Q Oh no, you haven't done that?

A If it's—if it's—depends on how you use the term medicine.

Q All right. I don't want to debate with you about the meaning of the term medicine either. For your testimony at a deposition or trial you're paid $2,000 a day?

A That's my fee, yes.

Q You agree with me that the FDA has determined that the use of Phenergan is safe and effective consistent with the labeling that we've been talking about today, correct?

A The—it's still approved by the FDA, yes.

Q Well, in your files there is a letter from September of 1998 from the FDA to the company [46] saying the labeling that we're talking about here today is approved. Use it. Correct?

A Well, it says it's approved.

Q Okay. And we can agree that you disagree with FDA's conclusions?

A Yes.

Q Can we agree that since that letter in 1998 FDA has again on several instances reaffirmed that it is appropriate to market Phenergan with the labeling that we have here today?

A I don't follow what you mean by—

Q That there have been other approvals of the labeling of Phenergan that's at issue here since 1998. Or let me—maybe what's confusing is by my use of the word Phenergan. You understand that Phenergan as a generic product, correct?

A It is now I believe. Promethazine.

Q Right. And that there were other companies in this country who market promethazine as well as Wyeth who used to manufacture it?

A I understand that now.

Q And there have been companies who have sought approval from the FDA to market it using this label since 1998?

A I don't know the specifics.

* * *

[48] Q You didn't put into that search engine promethazine to see what's available from the FDA today on this product?

A No, I didn't.

Q Now, I think you testified—well, you've testified that you don't believe the benefits outweigh the risks for—

A No, the benefits do not outweigh the risks, yes.

Q But you agree Phenergan has some benefits?

A Yes.

Q Okay. And you actually found in your file a couple of secondary sources that you pulled out and copied and marked that say promethazine is an effective drug?

A Oh, I'm not arguing that.

Q That's great. Okay. We're making a lot of progress. You've offered the opinion that the labeling was inadequate?

A Yes.

Q But you will agree that the risk of inadvertant intra-arterial injection was quite thoroughly discussed in a package insert for Phenergan, correct?

[49] A The risk—yeah. I think so.

Q Okay. And you believe that a physician should read every section of the labeling, correct?

A I believe so.

Q And I'm sure probably everybody here agrees with that. And I think when Mr. Rubin was talking with you, he laid out with you a hierarchy of provisions in a labeling and I think that that comes from you. I've seen that in other testimony you've given?

A Yes.

Q At the top of that pyramid the most important thing is a contraindication, correct?

A That's the Thou Shalt Not part.

Q Right. And you agree with me at the very top of the pyramid there is a Thou Shalt Not about intra-arterial injection of this product, correct?

A Oh, yes.

Q And at the top of this pyramid there is also a statement that says "Preferred route is intramuscular, not IV." But it doesn't prohibit IV use. We're not contending that. Do you agree with that?

A Yes.

[50] Q I can give you the package insert if it—we've talked about the contraindication section the Thou Shalt Not?

A Yes.

Q The next section you said in your pyramid, your hierarchy, are warnings?

A That's correct.

Q There is a section here in the warnings, its own section about inadvertant intra-arterial injection, correct?

A You're in the warning section, is that correct?

Q Yes, I am. There is a bolded top of the section, bottom of the first column of the label?

A Oh, okay. Yes.

Q Okay? And it discusses the risk of intra-arterial injection at length, doesn't it?

A Yes.

Q It talks about the close proximity of arteries and veins? In places where intravenous injections are commonly given?

A Yes.

Q It says that extreme care should be exercised to avid perivascular extravation or inadvertant injection, correct?

[51] A Right.

Q You understand that what happened here is that there was an injection into the artery, correct?

MR. RUBIN: Objection.

MR. HOFFMAN: This goes back to the stipulation yesterday, your Honor. I mean I—

MR. RUBIN: He can say what he understands.

THE COURT: I didn't—I think this is the wrong witness for this question. All right? He wasn't there. He doesn't know so I'll sustain the objection and ask you to continue.

MR. HOFFMAN: Okay.

Q You were asked some questions on direct about your understanding of what happened on April 7th, 2000, correct?

A Yes.

Q And the judge just pointed out you weren't there.

A Yes.

Q But you did read some depositions, right?

A Yes.

Q You read Diana Levine's deposition, the

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[Testimony of Jessica Fisch]

[62] goes by that I don't think about this horrible accident. And no matter how awful I felt during this period of time, I've always felt completely self-indulgent because I know the amount of pain and misery that this woman has been forced to bear because of this accident. There's not a day that goes by that I don't feel a great sense of grief over it. It's probably the worst thing that ever happened to me in my life.

Q Do you feel like you have any responsibility for what happened?

A I feel like I was the hand of God. I feel that—I feel that a tragedy happened when I was trying to help somebody when they had come to me for help; when they trusted me to give them help; when I trusted my own abilities to try to alleviate her pain that day. And I—I hope nobody ever—I hope none of you ever has to be in the situation. It's been almost a living hell.

Q You saw Diana on April 7th. I'm going to go back to what happened. You wanted to tell Diana that, what you just said?

A How badly I feel?

Q Hm-hmm.

A I don't have the words, but I want you [63] to know that every day for many days it's the first thing I think about. For a year there was a time when I wouldn't be able to use my right hand to do things. I couldn't—I couldn't focus. I couldn't sleep. I kept thinking about what had happened and how much pain she's been in and how much suffering happened because of this. I would have gladly cut off my arm. I would have given her my arm. I would have killed myself if I could have at times.

Q What was her condition on April 7th?

A She—she had come to the clinic in the morning. Diana had severe migraines. Migraines that were almost intractable in nature. She would not only be in terrible pain, she would not be able to sleep, she would be vomiting, she couldn't bear light or sound, and they happened fairly regularly for her. She really had been a good patient. She had been trying every possible way to do medications to prevent her from getting headaches.

Q When you saw her on April 7th what was her condition?

A Well, she had been seen in the morning and was treated for her migraine headache earlier that day and she had been brought back to the

* * *

[65] Demerol.

Q Why—what's the Demerol do?

A Well, Demerol is a narcotic. It's used for migraine headaches or severe pain. Migraines that Diana had in the past had been treated with Demerol and it had worked well.

Q Why did you decide to give it to her intravenously?

A Well, she had had an injection of intramuscular Demerol and Phenergan in the morning and it hadn't worked at all. So I felt that in order to give her some relief, that I would give it intravenously and try to get it in a more effective and swifter manner.

Q Have you given—are you authorized to prescribe and administer narcotic pain medication?

A Yes.

Q And how frequently have you done that over the years or weeks?

A I—probably given upwards of 75 IV injections of Demerol and Phenergan in the last ten years.

Q So you also decided to give her some intravenous Phenergan?

A Well, yes. I mean I was starting an IV, [66] and since I was going to be giving her the Demerol IV, it

didn't make any sense not to give her the Phenergan in the same route.

Q What's the Phenergan do?

A Well, Phenergan is a drug that's used for a number of things. It's basically used in practice for, you know, nausea and vomiting.

Q So—

A Sometimes.

Q Why do you give it—I know Dr. Matthew testified to this, but why do you give them together?

A Well, sometimes Demerol can make people more nauseated when they get it. Certainly that day Diana—she was getting dehydrated. She had been vomiting so much she couldn't keep anything down so she certainly needed something for vomiting. The other thing is she hadn't been able to sleep because of the pain and often Phenergan, which is an antihistamine, it can cause some sedation and it can help people sleep.

Q Is a prescription for Demerol and Phenergan common for the treatment of severe migraines?

A It was the standard of care in our [67] clinic. It's the standard of care in many hospitals, and many other sites.

Q Now, you decided to give her 50 milligrams. Why 50 as opposed to 25 or 75?

A In the morning she had gotten 25 milligrams of Phenergan and it hadn't worked so I increased the dose. And since it was in keeping with what was in the product information, I didn't have any second thoughts about giving her 50.

Q And how did you get the medication? Who set it up for you?

A I asked our nurse Pam Woodworth to go get the medicine. She went and got an IV set and the medicine I was going to need.

Q And why did you decide what method—we'll talk about the specifics in a minute—but what method of IV administration did you use? The free-flowing or the push method?

A I gave it to her by IV push through an infusion set which was in keeping with what the instructions were for the Phenergan.

Q Why did you make that decision as opposed to setting up a free-flowing IV?

A Well, you know, at the time I was anticipating just trying to get away to get the [68] medication into her in a swift and timely way. We usually set up a hanging IV like if somebody's had a heart attack and you're going to start an IV because the person's going to need ongoing treatment through that IV placement. But for Diana it was just a matter of, you know, five minutes worth of medication administration so I didn't go to the trouble of hanging an entire IV set.

Q What did the LPN bring you?

A Pam brought me—she brought me a tourniquet, she brought me alcohol prep pads, she brought me gauze, she brought me a syringe, a 3 cc syringe that had 2 cc's of Phenergan in it. She brought—

Q One second. I think that's it. Right. Why don't you open that up.

A So this is a tourniquet which probably most of you are familiar with and alcohol pads.

Q Keep your voice up.

A Alcohol pads. And this is a butterfly infusion set which is customarily used. And the medication came in syringes like this with the needle. And usually what happens is the nurse will take the needle off before giving it to me. So there was 2 cc's of Phenergan in one of these. And **[69]** then another 3 cc syringe there was the Demerol.

Q Let me just ask this. You got a syringe with the Phenergan in it?

A Yes.

Q How much fluid did that syringe—would it have held if it were full?

A Up to where this barrel is.

Q If it were full it would be 3 cc?

A If it was full, it would be 3 cc's.

Q And how full was it?

A It was this full, 2 cc's.

Q Okay. So what is the significance if you're administering Phenergan? What is the significance of there being 2 cc's of liquid in that syringe she gave you?

A Well, the Phenergan that we had at the time came in what's called the Tubex.

Q There is an example of a Tubex here. The jury has seen it, but I'll show it to you.

A Tubexes come like in a cartridge like this and they're filled with a certain amount of medication. And they lock into a device that has a plunger on it so that you can give the person an injection.

Q Why didn't you use the Tubex with the [70] needle on it and just plunge that into her vein?

A Well, one of the—

Q As opposed to having it transferred into a larger syringe?

A Well, one of the things that's nice about using a butterfly is that you can place it in the vein and then you can stand back a little bit from the patient. And even if they move a little bit, it's not going to affect the injection, like if you have a needle directly into a vein, if you're mainlining something. The fact that it has tubing also lets me see that blood is coming back into the tube normally from a proper placement.

Q When the blood comes back into the tube after you've placed the butterfly, what does that tell you?

A It tells me that things are where they should be in the vein because in pulling back on the syringe, which is—can I show—

Q Yeah.

A Okay. So what we do is have this in a vein and then we pull back—

Q Let me hold it for you. The eggplant disappeared here.

A What we do is pull back and blood will

* * *

[73] well.

Q So why did you decide to use this butterfly infusion set as opposed to a—was the free-flowing IV method—would that have been safer?

A I believe it would have been safer.

Q Why?

A Well, God, there's a couple of reasons. You know, if you have a hanging bag of saline, you've got more volume of liquid that's going into the vein probably at a fairly good flow. If—if the catheter were placed so that there was inadvertent injection into an artery, you know, there would be back pressure on the catheter so that it wouldn't flow in. You know, also I don't know if anybody has ever seen an infiltrating IV siting, but it forms a bolus, a bubble, under the skin if something isn't placed correctly. And with a large volume of saline in a hanging IV, that would be easier to see than if it was just a tiny amount of volume from the Phenergan itself.

Q So if you let the—

A IV run.

Q —before you put in the medication?

A Right. You would see if it was [74] infiltrating. And if you were in an artery, it would cause back pressure and wouldn't run correctly.

Q So why don't you use the free-flowing IV? I think you've answered that because you wanted to—it was just a single dose?

A Right. It was just a single dose. I just wanted to get the medication in in a quick and effective manner.

Q So can you explain why the use of the butterfly infusion set is okay and consistent with the instructions?

A Well, it is consistent with the instructions. It says so in the product information, if you read all the way down, that it can be administered through, you

know, what they call a rigid needle. It says that you have to be careful, and I am careful, and I was careful that day. So I feel that it was consistent with how the product described it should be administered.

Q People have talked about aberrant arteries. What knowledge or awareness did you have of a possibility of a misplaced or abberant artery at the time you were doing this injection?

A It never crossed my mind.

[75] Q Why not?

A You know, there was no mention of it in the product information. I had never thought that—I was using a very small needle and I was in a very shallow vein, I just didn't know that there could be an aberrant artery.

Q Well, didn't you take anatomy in your courses?

A Yes.

Q Wasn't there a mention of aberrant arteries along the way?

A No. There's only about a three percent aberrant artery occurrence; just wasn't something that I was aware of at the time.

Q There has been conversation here about whether Diana complained of pain. What is your recollection?

A I remember she said it was—she said "It burns," and, you know, I glanced up and I—and I looked at how the medication was going into her arm. And everything seemed the way it had always seemed and I'm used to people saying that medication hurts when I inject it. It's something that happens probably

every time I've given a shot so I told her "It will be over soon."

[76] Q How long did it take you to inject this medication? Phenergan?

A Probably about three to four minutes.

Q And did she complain of pain throughout the entire process or just at the beginning?

A No. She didn't complain through the entire procedure.

Q Why didn't you stop?

A Well, I—I—I looked—I looked at the IV site and it looked fine. It looked like the Phenergan was flowing in normally. And again, you know, it wasn't like she sat bolt upright and ripped something out of her arm. She said it burned and I just thought it was—I mean it's just crazy to have that phrase be the reason why you should be worrying about an IA injection. I mean it just—it's all over the place. I mean how can I make a judgment call on somebody who's writhing in pain with a headache and saying that the medicine burns? Does it burn like a lightning bolt going through your—I mean it's just so interpretive. I mean everybody complains of pain usually when they're given an injection. It's just a vague instruction. I—certainly it would get my attention now knowing what I know, but at the [77] time it just didn't seem like she was screaming in pain.

Q After you completed treating her did she leave?

A Yes.

Q And she came back?

A She was brought back, yes.

Q About four o'clock?

A Yeah, she called and said that her arm was cold and I told her to come right up.

Q Were you there?

A Yes.

Q And did John Matthew come in?

A Yes.

Q And what involvement did you have in her treatment after she came back at four o'clock on April 7th?

A Well, you know, we examined her and her arm was blue and cold and she was very uncomfortable.

Q About the headache or the arm?

A About her arm.

Q How was her headache?

A I really don't remember.

Q Go ahead.

* * *

[81] excuse for taking somebody's arm and having some kind of an extravasation injury that means that they lose their fingers or their arm. It's nausea. It's not—this isn't—this isn't a heart attack, this is somebody who's sick to their stomach.

Q Does Wyeth send representatives to the Health Center?

A I see a Wyeth representative once or twice a month.

Q And what goes on? What's the relationship between the clinicians like yourself and the—what do they do, these representatives who come by?

A Well, their job is to get you to prescribe their medicines because that's how the company makes money. Supposedly it's to keep us abreast of information and to let us know about any problems that the medications might have had. The person—

Q Who—go ahead.

A The person who was the rep for Wyeth Pharmaceuticals—we've got at least three pharmaceutical reps from Wyeth that come every month right now—but at the time that this

* * *

[86] just setting it up. That doesn't include starting the IV.

Q Okay. But there was a 20 minute period—

A I went to see other patients, scheduled patients.

Q You went on to see scheduled patients?

A Yes.

Q You testified earlier that you used the butterfly because of the convenience sake for Diana, as I understand it, that she was just going to be there, get the shot and go along back to her home?

A Yes.

Q And does the butterfly—could you take out the butterfly if you would please.

A I think I might have been playing with this.

MR. RUBIN: I don't think you need to take the needle off.

MR. O'ROURKE: No, I just want the butterfly. That's why it's called a butterfly because of the two little wings here?

A Yeah.

Q Now, do you normally tie those down with [87] a tape or with adhesive when you put them for an antecubital injection?

A Sometimes.

Q Why do you do that? Why do you tie them down with a tape?

A Well, if you're putting it into a very superficial vein and there's a lot of potential movement you might tape it down so that the position of the butterfly isn't jostled.

Q And is that good medical procedure to do that?

A I don't think I could use an expression like good medical procedure.

Q Well—

A It's—

Q Let me ask you what the standard of care is, that you should tape it down?

A I dont know that that's the standard of care.

Q But in any event in Diana's case you didn't do that?

A I did not.

Q Do you have some judgment as to what percentage of the cases that you have used this butterfly

that you would have taped it down in the [88] patient where you were going to give the injection into the antecubital area?

A I would say that the only time I've taped down the wings on an infusion set was when this was attached to a hanging IV bag which usually in our practice was to administer an IV antibiotic over about 20 minutes. The rest of the time neither myself nor any of the other practitioners in my clinic routinely tape down the wings of butterflies when it was used just for a very short infusion.

Q Would you use the butterfly that—if you were using a hanging bag or would you use a different type of infusion?

A Sometimes we will use butterflies, and sometimes we use intracaths.

Q You didn't actually mix the medication, did you, or prepare the medication I guess—

A No.

Q You said Pam Woodworth did?

A Yes.

Q Now, have you had an opportunity since the time that this incident happened to talk with Pam Woodworth about this?

A We've discussed it. We—I'm not sure

* * *

[90] A I read that, yes.

Q And did you read that she also said—referring to page 123 at line 16—"it was one of the most extreme pains I've ever felt"?

A I read that.

Q All right. And did you read that she said that you said that "you just got to stay there and be quiet so you don't dislodge the needle"?

A I don't remember that part.

Q And—but in any event, did it ever cross your mind at any time to stop injecting the medication?

A I briefly thought about it. I, you know, I looked down at the IV site and nothing seemed amiss. And although Diana, you know, in that statement she said she was screaming, I don't remember that she was screaming. I remember she was speaking in a normal tone of voice and said "It burns."

Q And did it take you two minutes to inject the Phenergan?

A Probably a little bit more than two minutes.

Q And can you give us some judgment then as to how long it took you to inject the Phenergan?

[91] A About three minutes.

Q And you were aware at that time that the literature, the labeling of the drug, says that if a patient complains of pain you should stop the injection?

A Yes.

MR. O'ROURKE: That's all I have. Thank you.

THE COURT: Anything further, Mr. Rubin?

MR. RUBIN: No. Thank you.

THE COURT: Ms. Fisch, thanks very much.

MR. KIDNEY: Can I have a minute, your Honor?

THE COURT: Absolutely.

MR. KIDNEY: Your Honor, our next witness will be about two or three minutes.

THE COURT: Okay, everybody stretch for a minute.

MR. KIDNEY: Thank you. Call John Gailmore to the stand.

JOHN GAILMORE, duly sworn

Direct Examination by Mr. Kidney

Q Good morning.

A Hi.

Q Could you state your name please?

* * *

[Testimony of John Gailmore]

[93] the purpose was to—to celebrate children and childishness and the creativity that is inherent in kids and to encourage them to never forget it and keep it up.

Q John, do you know Diana Levine?

A Very well.

Q How do you know her?

A Well, we've known each other almost since I moved to Vermont in 1977. I went to see her sing and I heard her on WDEV often, both as a solo artist and with her sister Liz.

Q Liz is sitting right here?

A They had a magnificent duo called the Winn Sisters, oddly enough, and they wrote songs and sang and it was a totally unique and joyous sound.

Q Did you ever play on the same bill with the Winn Sisters?

A Quite a bit, yeah.

Q So you've seen Diana perform?

A I have.

Q How was she as a performer?

A Well, she exuded warmth and joy and I very much related to her style and her attitude because she too found—had discovered why she's **[94]** here and what she's on earth to do. And so have I. And there's nothing better than that sensation to have—to have discovered what you're here for and to be able to pursue it is just beyond description.

Q John, you've seen a video clip of Diana performing, is that correct?

A I have, yeah.

Q And I think she's playing "Mr. Postman"?

A Correct.

Q Do you think that that video clip is a good example of Diana Levine as a performer?

A Oh, it's an excellent one. You can see—you can just see in her body language and in her facial expressions and the whole—just the whole performance, you can see the joy in her. And you know when someone is doing something that is a natural thing for them to do and is their passion, you can see it. It's very evident.

Q John, I want to show you Exhibit—Plaintiffs Exhibit 32. Is that in fact the video clip that you were shown?

A It is.

MR. KIDNEY: Your Honor, I move to introduce Plaintiffs 32 and to show it to the [95] jury.

MR. O'ROURKE: No objection.

THE COURT: Okay. Thirty-two is admitted.

(Plaintiff's 32 shown to the jury.)

Q John, could you just comment on that clip in terms of Diana as a performer—I guess that was at the City Center in Montpelier concert?

A Yeah, I'd love to comment on it. I see myself in her because it's hard to describe the feeling of—of doing the natural thing and doing what you're supposed to do in life and of just affecting people and making music and just—I'm not a religious man, but you know, of carrying forth and of pursuing what you're here to do. And you can see it in her and I was looking at her hands, too, as I watched the video, and I was particularly looking at her right hand, which is the really important hand in terms of—of carrying through from the heart. It's the one that—that controls the rhythm and the whole feel of the song. The left hand is playing chords, the right hand is the joyous hand. That's the one that's—that's doing the picking or the finger picking and is the real controlling hand in terms [96] of the feel of the song. And it was beautiful to watch.

Q Well, speaking of hands, could you talk about the creative process and how, if at all, hands are involved in that?

A Well, everyone creates differently. I have written songs where I've just written a poem and then put to music. I've also written songs where I have just been in my studio fiddling around with the guitar. And the chords, the progression of chords and the rhythm conjurs up a subject; just the beauty of the chords and

the rhythm conjurs up the subject. So oftentimes I will create through my hands. I will—I will—just my hands will be creating independent of anything else. They'll just be creating and that will make me think of a subject and will cause true emotions in me and that will make a song.

Q Well, for someone who is a singer/songwriter like Diana, then what does the loss of a hand mean?

A It means that you—you lose an integral part of your creative process. And your—you lose an essential part of your act to express what you feel in your heart and there is no [97] greater loss than that. It's a paralyzing—emotionally paralyzing thing to lose. And I will reiterate especially the right hand in a guitar player or in a bass player, which Diana does both, because if you've ever seen—well, you saw her hand playing bass, really you can do wonderous things with that right hand and losing that all you can do is play chords and imagine the rest. So it's a terrific loss.

Q Now, were you familiar with the Re-bops?

A Yes.

Q What can you tell us about them?

A Well, you know, to a great extent, the Re-bops do exactly what I try to do with kids is to make them feel like stars, and to just boost their self-image and to give them the opportunity to flourish and to be creative and to sing and to do what kids do naturally, which is to sing songs and perform. And kids are hams by nature. And so the Re-bops gives them a chance to do all those natural childish things.

Q So in your opinion, John—well, strike that. I'll just ask it this way. How important over the 27 years that you've known Diana was her music to her?

[98] A Well, I'm not sure there are words to describe that. It meant everything to her. You could see it in her performance. You could—we talked often about how lucky we were to be doing music for a living, how lucky to have found our passion and to pursue it, to be able to pursue it. And it's a loss of a fundamental part of your being. She still had a lot of love around her from her friends and her family, but to lose the ability to make music and to express her heart is irreplaceable.

Q In terms of expression, I mean as a non-musician, does a musician express both joy and sadness through their music?

A Oh, all of it. Yeah. And you can express—I mean the arts is the best vehicle for expressing emotions. Music more than any other I think because it's immediate and it goes right to the spine and you can express profound sadness and tragedy and the ultimate joy and everything in between. There's nothing that music can't express emotionally.

Q Well, would this be an example of the joy?

A Oh, absolutely. You can see it in her.

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[100] sadness and to make—to make beauty out of it. And also to express hopefulness at the same time.

Q So how is Diana going to get through this tragedy without her music?

A Well, Diana will because of her strength. Her life will never be the same. She'll never be able to make music the way she did. She'll always be able to make music because of the music in her, but it will never be the same without that hand. That is a—a fundamental basic loss that can't be replaced. She will get through it because of the love of all of her family and

friends around her and her music will still be beautiful, but the process will be different and it will—her music will never be as close to her heart as it was because of the loss of that conduit really which is what a hand is, an arm directly from the heart.

MR. KIDNEY: Thanks, John. All I have.

MR. O'ROURKE: We have no questions, your Honor.

THE COURT: Mr. Gailmore, thank you very much for coming.

MR. RUBIN: If the court wouldn't mind, we would like to break a little early.

* * *

[Testimony of Jessamin Levine]

[105] the Re-Bop business, what was it?

A Well, my mom was just like really brilliant with kids. I mean she could bring them into any space and just draw—evoke these amazing things out of them, spontaneity, playfulness and the kids were really a huge part of the creation of the music. And it wasn't like she was a dictator. She was definitely a collaborator. And there was this—one of the albums is called "Raised on Rock and Roll" and it's like "Raised on rock and roll, raised on rock and roll. I was born to boggie, I was raised on rock and roll." And that was like—my mom and dad wrote that together and it was really pretty autobiographical to me. I was.

Q Raised on rock and roll?

A Yes.

Q So obviously the Re-Bops meant a lot to you. What did they mean to your mother? What did the Re-Bops mean to your mother?

A It was really her life. When she found this way—she was very lucky to find this way where she could incorporate her love of music and her love of children and there were these perfectly interlocking loves. And then without her ability to make music, like she used to—there's this **[106]** dangling love and I'm sure she'll find ways to work with it, but it's definitely not the same.

Q And your dad was in the business, too?

A Yes. He was the engineer.

Q So how about outside of the Re-Bop business, what was your mom like as a mom?

A She was just so active and artistic and giving is probably the number one word I would say is giving, giving, giving, always thinking of others, joyful. She did poetry and pottery and photography and athletic things like skiing and tennnis and swimming. Just very well rounded, very exuberant person.

Q I mean we all use our hands a lot obviously, but was your mom—how would you describe her in terms of her relationship with her hands and who she was?

A Well, I think about my birthday parties and every year there would be some theme that I would pick out and she would just go all out with them in the craziest ways. Like one year the theme was rock and roll and there was this cake that was probably as long as this stand, maybe even longer. It was turquoise with a lightning rod. It had like Reese's Pieces knobs and licorice strings and it

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[108] supposed to be the one calling me up at college and saying "Are you eating well enough?" But she knows I have everything prepared for me there. And whenever I call, I'm like "Are you eating well?" Because she really can't cook for herself in a way that's nutritional. And like I came home and all the heavy, cast iron skillets were gone, which were like the best skillets to cook with, but she was just using them because they were there and it was hurting her even more her remaining arm, the tendonitis she had. So she just got rid of them.

Q Has she baked at all since this tragedy?

A She has tried to. It still tastes good. It just takes a lot longer and anticipate the hunger. And she made Christmas cookies this year. Every year she makes really elaborate Christmas cookies to hang on the tree, and I could hear like noises of frustration coming from the kitchen, but so it's not like it was—it's a joyful process anymore. It's a lot more grudging. So she doesn't do it basically.

Q I think you talked about this a little bit. Could you just tell us about how big a part music is in your mom's life?

A It's just so huge. When she's soaring, [109] when she's joyful, that's how she expresses that. When she's down in the gutter, that's how she resonates with that and rises out of it. So it really was her therapy and it—I mean I've learned just the power of music to heal is so immense and I use it in my life. But I just remember ever since I was little, whenever my mom seemed sad or something, she would just go pick up her guitar and work through it with her music. And her album "Sink or Swim" after my dad died was like—that's what

she was working through, her grief, and I don't know how she would have done that without her music.

Q Do you play music?

A I do.

Q What do you play?

A I play mostly guitar. I'm trying to learn bass a little and a little drum set, a little hand drum and steel drum.

Q What's your mom play?

A Right now?

Q No, what did she play?

A Oh, she played bass and guitar and piano.

Q Are there many female bass players out [110] there?

A No. There should be.

Q So music was a big part of your family life?

A Yeah, and we used to play music together. Like on the songs I'd written she would make up bass lines and I would be like well, I don't like some of her rules, but if she makes bass lines like that, she has to have some authority, you know.

Q Did you—I asked you to show me some pictures that kind of show you and your family and the musical connection. Did you give me those? I'm showing you Plaintiff's Exhibit 37 and 38.

A Yes.

Q Okay. Was there also another picture which we've already talked to Mr. O'Rourke about—and we don't have a hard copy, your Honor, but we'd call it

Plaintiff's 39 and we'll get it in—we've got it on the screen, but we don't have the hard copy. We lost that.

MR. O'ROURKE: No objection to that.

THE COURT: Fine. So 37, 38, 39 are all admitted.

Q We're going to put these up on the [111] screen and you can just tell the jury about these pictures. And so we've got this picture. Can you tell the jury about this?

A That—

Q Wait, Mr. Rubin has to move for you I guess.

A That is me, my mom, and my dad and I was raised on rock and roll, and that's evidence of that. And that was before I started playing guitar, but I started pretty young, when I was like eight or nine.

Q All right. And why don't we go to the next picture. That's going to take a second.

A That is my mom on the bass and me on the drums. And I remember I think my band teacher at school—I had played bells, too, actually and he said oh, you'd be a really good drummer. And I was kind of like, well, I've never seen girl drummers before, even though I was all about girls, too, you just—my mom encouraged me so much to play the drums and—and we jammed together.

Q So did you make a lot of music with your mom over the years?

A Yeah.

Q Okay. And we'll look at the last

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[114] in. And I mean I'd seen her in pain over the loss of my dad, but this was like physical pain and she sounded like she was having a baby. It was really traumatic and her arm was swollen—so swollen. Every day it would get more and more swollen and blue and I was like—I would massage it and put water over it and try to take care of it, but I mean we just all could sense that something was really wrong then. The pain was so great and it was hard because I knew that no matter how much pain she was showing that she was in, she was in a lot more pain than that. She's always like—she's always tried to shelter me from pain.

Q How about fear? Do you remember any of that?

A Well, a lot of fear, just not knowing exactly what was going on and and having some sense of what it would mean to lose her arm, but never—never being able to predict how many different ways it would affect her.

Q And that was when your mom was at home after the shot of Phenergan?

A Yes.

Q How many weeks was that?

A I don't know. To be honest, like all [115] the details of that time, many are very blurry for me because I was just very emotional and kind of trying to be a little uninvolved so I didn't break down.

Q Did you ever see your mom up at the hospital up at Dartmouth? Or down at Dartmouth I should say.

A I went a few times. She really didn't want me up there again protecting me from how horrible it was, but one of the times I went I brought members from

Village Harmony and we serenaded her and she just loved it. She was crying and smiling and—

Q What about when your mom got home from the hospital? What was that like? After the amputation.

A That's when it really started sinking in because she would be trying to do all the things she ordinarily did and she just couldn't do them. At first she couldn't even lift her—like had very serious mobility problems as well and she was doing physical therapy for that, but I mean she couldn't tie her shoes so she had to go buy Velcro shoes. She couldn't open jars so I was opening jars for her. I felt like the principal like [116] helping the kindergarten kids at school or something. It was just very strange and surreal because the roles were really reversed a lot of times. And to have to be the mother of my mother was bizarre and I never—I just became so grateful for my arm and I missed her arm so much like her—both her arms being able to rub my shoulders or play music or—I mean it was amazing how many—how many times I was just like wow, what would I do if I only had one arm in that situation?

Q What kind of things couldn't she do?

A Well, she couldn't do—she had to totally reconceive of the way she did the most basic things like even getting up in the morning. She couldn't make her bed so she had to have someone help her with that just like putting the sheets on the bed. Buttoning up her shirt or getting her clothes on. Even today I was just struck by that again like trying to decide what to wear. All of the girls like getting together to try to look—I mean we were professional, but just how long it takes her to get dressed is amazing. And on top of that, I mean she always used to just whip through the mundane or the [117] everyday things, you know, and like cooking and

cleaning and now she can't really do any of the creative things because it just takes so much longer to do all of the basics.

Q So now it's almost four years later, right?

A Yes.

Q Tell us what you think your mom has lost as a result of this tragedy.

A I think she's lost a little bit of her mind. I mean a part of her is gone. It's like her best friend in a way, her arm, because that's what allowed her to make her music and to do all the things she loved, but also just to do the things she needed to do. She's not the same person. Like when you're sitting next to her, you can feel her grief and you can feel everything she's been through and she still tries to be strong and you can admire her for that, but she's a totally different person.

Q Does your mom ever get bitter or angry?

A No. And that's just been a very valuable lesson to me. She's so forgiving and—if she ever has had resentment, I have not seen it before she let it go, so I couldn't tell you.

[118] Q How does she deal with it? How does she cope?

A I think she—she just takes triumph in the little things that she is able to do. I mean it reminds me of like the Sesame Street episode that I had taped from when I was little where the little kids learn how to put on their clothes and they're so excited and she is so excited when—or when she finds new ways to—that makes things easier. Like she found this contraption that has a suction cup and a nail cutter, nail clipper attached, too, so now she can clip her nails. She just takes joy and she bounces back a lot, but it's because

like she's fallen. She has to trip over and over again. It's like oh, I can't do this the same way anymore. She's tried to rearrange the house so everything is easier. She leaves the doors a little bit open so there isn't so much friction because she has to be so careful to protect her remaining hand, but I don't honestly know how she does it. I don't know how I would do it.

Q So you think your mom will make it?

A I think she'll make it, but it's just going to be so hard and I mean she—I just think [119] of her as such a joyful person. And when I think of all the things that she used to take joy in, everything is so difficult now. And I don't know how she could keep on shining through that. But when she sees the most depressing movies she will be like "Oh, I thought it was uplifting," and we're all like "You're crazy," but it's because of endurance and she knows—she sees that reflected because she has had to endure so much and she sees—she gets a kick out of symbolism and stuff like that. So when she saw the movie "Finding Nemo" because he has like this little fin, he was born with one tiny fin, it's called his lucky fin, but he still goes on a huge adventure and swims through it and is strong. So she takes joy in stuff like that. But she stumbles so often and I don't think any of us can imagine what it's like for her. Especially losing her music. I mean that was her foundation, that was her rock that kept her sane and gave her the drive to keep going.

Q It also allowed her to soar?

A Yes, and to make connections with people. I mean a lot of her friends—most of her friends are musicians and that's what they would do together. So she's going to have to reinvent her [120] relationships and the way she moves through space, just the physical reality

of it, and invent a whole new conception of herself because so much of her self-image has been affected so much by this. And she still does go out and makes public appearances and is involved in the community, but it's so much harder for her because she's not symmetrical.

MR. KIDNEY: That's all I have, Jessamin. Thank you. Mr. O'Rourke might have a question or two for you.

MR. O'ROURKE: We have no questions. Thank you very much.

THE COURT: Thanks very much.

MR. KIDNEY: Call Steven McArthur to the stand.

STEPHEN MCARTHUR, duly sworn

Direct Examination by Mr. Kidney

Q Good afternoon.

A Hello.

Q Could you state your name?

A Stephen McArthur.

Q And where do you live?

A In Berlin.

Q Who do you live there with?

A With my wife Ricki.

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[Testimony of Stephen McArthur]

[130] as well as a fellow musician and a former business colleague. Can you tell us what she was like before her amputation?

A Unstoppable. Overwhelming. Just on the go. Just an amazing energy. Both my wife and I talked about how we just couldn't keep up with her. We never knew where she was going next, what she was doing next, what project she was doing next. Musically she was doing a lot of other things. She was playing with other bands. She was playing with small groups, some large groups. I was invited at one point to—not long before the accident happened I was asked to play with her up at a big club in Burlington with a band she was playing with, which was a nice honor for me to be asked to come and play with her. But yeah, she was just full speed ahead with the record business.

Q How about outside of music? What kinds of things did Diana like to do?

A At one time she was a potter. Still a kiln I think on her porch. Her photography, her—some of her writing, her song writing, which is in and of itself poetry, was always something she—she did cooking. We'd go over and have these wonderful meals. Her kitchen is one of these [131] eat-in Vermont kitchens in an old Vermont house. Active. Lots of friends, people over at the house all the time. She was on the go all the time.

Q I want to talk about the year 2000. Did you see Diana up at CVH?

A Yes. We got a call saying that something had happened. We didn't know exactly what it was. I think her sister called, but we—we went up immediately, as soon as we heard she was there, and first thing we noticed was her arm and how it was wrapped up and you could just see the fingertips. They were dark I mean at the time we didn't know what was happening; the doctors didn't even know what was happening. Every-

body said oh, this is just going to get better, but as we all know, it didn't.

Q Did you see her up at Dartmouth? Or down at Dartmouth?

A Yeah, we saw her a few times at CVH, then we heard she was going to be transferred down there. The first time we went there, it was very clear that the doctors—this was not something that was going to recede. That what they were doing was trying to figure out how far it was going to go before they operated and took off whatever [132] they had to take off. At first when we talked to Diana the first time, it was well, maybe it would be just up to the fingertips, or the next time it was um, maybe the knuckles, and then oh, maybe just half the hand or maybe to the wrist. Well, it wasn't even the wrist, it just kept on going. So every time—every time we went just, you know, just—it just died a little more.

Q You were there. Tell us what the hand looked like over the course of this month at Dartmouth. Tell us what you saw.

A Black, bloated—I mean I don't even think—somebody used the word gangrene, but that's—you know, I've seen gangrene in the movies. To me that's what it looked like. It just looked like it was just rotting flesh. It was just awful. It was awful.

Q If you could just tell us what that whole experience was like waiting for those three weeks when she first got there, when they did the first amputation. Just tell us what happened up there, what it felt like, what you saw, what Diana went through.

A Yeah. I mean for us it was bad. But for Diana, we couldn't—we couldn't even get our [133] minds

around. She was sitting in this bed and dealing with this life altering experience surrounded by friends and family, a lot of pain, deathly afraid of any kind of needle because that's where it all started. They had to take blood tests, they had to give her medication, they had to use needles. And that needles in and of themselves became this—this—this like horror thing for her. So, you know, we would be there and they would come along, well, we have to take some blood and it was—she'd start shaking, crying. She was in pain. I mean for all of us being there it was one thing; for Diana in that bed it was something that none of us can—I mean I've thought about okay, well, if I lost my arm, I wouldn't be able to play sax again, but kind of big deal, that's like a hobby for me. I was thinking about her, something that was so integral to her existence, playing instruments. I just—I couldn't get my mind around that.

Q When you describe the hand, was it moving from the fingers up the arm or was it just black and as you described it all at once?

A Well, from the time we saw it at Central Vermont Hospital where the fingertips were black, **[134]** it just—it just kept moving. It just kept dying all the way up. And every time we saw her, it would be worse. And as it got worse, it got black and dark green and purple and just awful and of course it was painful. It's not like it had lost feeling. It was painful.

Q How much pain was she in?

A We—we could see that she was in pain all the time. You know, what they were giving her we didn't know. I mean those kinds of medical things we didn't have any—we weren't family, we could just be with her, talk to her.

Q Used the word dying. Was she watching parts of herself die in front of her eyes?

A Yeah, that's what was happening. And from what we heard was they were going to have to at some point make a decision of how much of the dead arm they were going to cut off. And they didn't want to operate too quickly because if they cut off this, it could still keep going and then they'd have to do—they wanted to do one surgery. That was what the doctors said.

Q So how was she taking all of this? What was going on? What were you witnessing her reaction to this was?

[135] A Incredible fear. It's so hard to describe. It's watching somebody you care about having her life altered so critically and at the same time being in such pain. The complete unknown of what the future was going to hold for her with—and then how much of it she was going to lose because she didn't have a clue, you know, how far was it going to go?

Q Did you see Diana after she got home from the hospital?

A Yes.

Q Did you make a point of seeing her frequently or was it just—

A Sure.

Q Tell us about that.

A Contrary to her entire existence before this, the one thing that struck me was one of the big decisions was what big new chair could be gotten for her to sit in. Diana was not the kind of person that sat around, but that was like a big deal, and understandable, but you know, what a difference. Here's some-

body who beforehand was like flying a hundred miles an hour and then the big decision was well, what comfortable chair could she sit in? It just—it was such a—for me it [136] was such a personal contrast of who Diana is, just that simple little thing to me was shocking. We went there. We would go for dinner. We'd take stuff. Probably a couple of months after she got home she said I want to show you something and she has a piano in her house and she got up and with her left hand played a piece. She got out a piece of sheet music and it was about 30 seconds long and she made it okay. She kind of turned to us with tears in her eyes and said there are not a lot of one-handed pieces for one-handed piano players. I mean I don't know how many one-handed successful musicians anybody has ever heard of, but I haven't heard of any.

Q You told me about something that happened at your house when you invited her over for dinner. Why don't you tell the jury about that.

A We had neighbors who have friends who come and stay from France in a log cabin on their land right on the Dog River. It's a log cabin that has no plumbing, no electricity, and these folks live there for two months every summer. They love Vermont so much they've come from France to stay here. And through a set of circumstances we

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[Testimony of Elizabeth Winn]

[142] she, being my older sister, definitely was the one to influence me. She took the piano lessons and so that made me want to do it, and she—everywhere she went and still—not still, but she would take her guitar around with her everywhere she would go, down on the dock—we grew up on Lake George—she would take it

down on the dock. So I'd follow her and want to learn how to play guitar, always wanting to do what my older brothers and sister wanted to do. So she was my main influence in music.

Q We've already heard a lot about your sister and what music means to her. I think we can skim over most of that, but you said something about your sister singing in the shower or something that I thought summed it all up. If you could just tell the jury?

A Um, well, what I said was a lot of us are closet musicians and we will sing at full voice and tilt while we're in the privacy of the shower, but for my sister, the whole world is her shower, she sings everywhere she goes. She brings her guitar—or did—everywhere she would go and she would sing and always, always, always, always composing and singing. So the world is her shower.

* * *

[144] Q You do that with one hand, right?

A Yes, but the thing that I think hasn't been said that I want to make really clear is that a lot of people say okay, she has one hand, she can still do this. But being the sister that lives next door and sees her every single day, I'll tell you she doesn't have—she doesn't have this hand a lot. She has severe overuse syndrome in this hand. She tries, as you've heard, you've heard about her perseverance. I've had to yell at her upon occasions to just put the pot down, you know, don't strain yourself. Let me do it. Let me help. So she has severe tendonitis in both shoulders and overuse syndrome. She has to wear a brace and, you know, the cold pads. And so most of the time she doesn't have either. And the prosthesis helps mostly with driving, but the prosthesis is enormously heavy and it adds to the ten-

donitis on this side of her body. And so I just want to make that clear. It's like yes, we're lucky she has the one hand and we're lucky she has the elbow, but in many ways, many times she doesn't have either. I don't know if I answered your question.

Q Well, yeah, I cut you off, but in terms of does she still enjoy painting after—

[145] A Yeah, so she still enjoys painting, but it's like everything. First of all, she has this—her left arm, which is her dominant hand is disabled as well. So it's very difficult, especially her hand, I would say it's like—it's almost like people who are crippled with arthritis, it's very painful. And so she—it's as Jessamin pointed out, the joy of it isn't there and it's so stressful that she becomes kind of this inertia and so she doesn't do it because it's painful mostly, also because it doesn't bring her the joy, but it's mostly because it's painful. She's in chronic pain, constant pain.

Q Now, you were—I had asked you about other creative things that she used to like to do before the amputation and she can't do now. And that's when I cut you off. If you could just continue on that.

A An amazing photographer. Again, just natural talent. She has an eye for composition. So she's done it for as long as I can remember. And even as a young adult, she had her own dark room with the developer and developed all of her photographs and they're just gorgeous. Just gorgeous.

[146] Q Can she still do photography now?

A Yeah, as you heard, the determination. She's determined. She's, you know, first she grieved and grieved and she would watch people taking pictures and just cry and cry and cry and "How am I ever going

to do that?" But determined she's trying to figure it out, so like she'll take her right limb and prop the camera up. I didn't mean to bring these for a camera prop, but you know, prop it up and then—and that's what happens—and then she reaches over 'cause the clicker is here and she'll click. So, you know, I bought her a little tripod and we'll play, but again, it goes back to this hand is still very painful and the effort that it takes to do that. Just the little day-to-day things she has to do like showering are all she can do. So to take pictures is just—she pretty much doesn't do it, but I know she wants to.

Q Liz, you talked about day-to-day things. Why don't we just jump ahead into that for a minute? At least in my own mind at least jump ahead. After the amputation have you lent assistance to your sister in daily living?

A Yes.

[147] Q And so you know what she can and she can't do. You've seen it first hand?

A I see the things she hides from her daughter.

Q Let's just go over some of these things. Let's start with getting dressed. Buttoning up a shirt.

A She basically can't do—I mean yesterday she was trying on one of my blouses and I noticed that I automatically was buttoning it for her. So I think she just kind of tries to stay away from outfits like that. But she can do it, but it's trying and because you have to button something, you have to, you know, first punch—most of us kind of do it like this, you open one hole and throw the button in. She has to do kind of both simultaneously. She can do it, but it's extremely painful and just frustrating. So she tends not—you

know—we buy our clothes differently. We shop together and we look for different kinds of clothes now.

Q How about putting on a bra?

A Well, I helped her with it yesterday and I help when I'm there and I know I can't go down there every morning and put her bra on, but when [148] we're together I do it for her. All I can say is try it because you—you know—it takes two hands. And to do it with one hand is like—is contorting—you know—hands and painful. It takes her I would say, when she chooses to wear one, because it's such a pain, it probably takes her about ten minutes.

Q Putting on socks?

A Same thing. It's—for most of us we it takes two hands. We open it up and pull it on and for her she has to shove her thumb in and kind of just kind of wiggle it in and it takes a good minute per sock causing pain.

Q How about putting on a belt?

A She doesn't wear a belt anymore. Again, for a belt you have to go around like this and she doesn't even bother anymore. She doesn't even bother wearing pants anymore because to put pants on you have to lie on the—it's similar like a big sock, you know, she has to basically lie on the bed and puts one leg in and stands up and puts the other leg in and again, causing pain and then the zipper, you know, again, think of it. You need two hands for that because you have to make it taut, so she'll put her elbow and then go like that. And [149] then the hooks, again, similar to a button, it just—she doesn't wear pants. She doesn't even—well, I won't share that—I won't say what else she doesn't wear.

Q Shoes?

A Shoes, we make sure she has Velcro sneakers. She can't tie at all, but again, similar thing to a sock. That to put on like rubber boots, it's extremely painful for her and takes her forever. She gets frustrated.

Q So what time do you leave for work in the morning, Liz?

A Around quarter to seven.

Q So you take much time getting dressed or are you just up and out?

A I'm up and out.

Q Take much energy for you to do that?

A Oh, no.

Q How about Diana, if she wants to get dressed in the morning and get out of the house, how much of an effort is it?

A It's huge. I mean every single step, starting from—starting from just when you get up in the morning, we think of the simple act of just making our bed, she doesn't do that. Even tucking [150] herself in at night, you can't pull sheets up.

Q We'll get to that, just okay, but getting dressed is a chore for her?

A It's a huge chore, yes.

Q Let's talk about personal care, shaving, women—how is it for her shaving?

A Well, when this first happened, I had to do it for her.

Q And why is that?

A Because she can't—can't do this. So she has a left arm so she can do her right armpit, but to do this

one, I needed to do it for her. So basically what she does now is just goes like this and, you know, just don't look on that side at her armpit.

Q How about flossing her teeth?

A For awhile she didn't do it at all and her teeth really suffered for it. In fact, I think she had one tooth that had a ten millimeter pocket and it had to be pulled. And so they found—similar to what Jessamin was describing with the fingernail cutters—it's a one-handed—it's almost like a little bow.

Q Like a violin bow?

A Like a violin bow, so she has that now.

[151] Q How about washing her hair?

A She puts the shampoo on her limb and then quickly before it falls off or maybe the second attempt, because the first one has fallen off, she just kind of quickly scoops it up and then she can do this.

Q Cleaning her fingernails?

A She doesn't do it.

Q Let's talk about some household procedures. Using scissors?

A Again, she basically just doesn't do it.

Q Why is that? I mean I can go like this with this hand.

A Because you have to hold it kind of—I'll do it with my right hand. You have to kind of hold the paper taut. And also again, that's why, you know, it's a small motor skill, scissors are in fourth grade. They're—just now they've just mastered it and so it's a small motor skill and she—this is what's painful. So it's the little

everyday things like that she just doesn't want to do, she has other people helping her with.

Q Opening the daily mail, the envelopes, you get every day?

A Again, she—I've seen her do it. She [152] gets the mail, sits down and puts her finger in, but for the most part she has help with that or just rips it apart. I've seen her use her teeth, too. She had mentioned that, that she does a lot with her teeth and she has damaged her teeth. They're all chipped in the front now. I mean like, for example, hold up a pair of pants because, you know, putting pants on a hanger, you have two hands for that. So what she'll do is put it in her teeth and go like this, so she does a lot with her teeth.

Q Can she hang clothes? Take a jacket off, take a hanger off and hang it and put it back up?

A It's one of the things that we helped her with. There are many, many things that we actually had to—it's like Jessamin said, it's like being a kindergartner, things you start over with and hanging was one of them, that she really wanted to learn how to do. And so she can do it, but it's a huge effort. So much effort that we just said, you know, it's one of those things don't worry about it. We just put some hooks up in her closet.

Q Because hanging is one of the things you have to use teeth with?

[153] A Yes.

Q Hold the hanger with the teeth?

A Yes.

Q And what about opening bureau drawers? You've got a bureau, you want to pull it out.

A Her whole house is not real expensive antiques, but farm antiques and she takes a lot of pride in them and loves them. But most of them have handles on either side or knobs and they're kind of funky. You know, the older drawers are harder to pull out, but she really loves them and so my father came and put knobs in the middle so that she can just pull it out and then it's more balanced, but we probably need new furniture.

Q Writing checks?

A Again, I've seen her do it and, you know, she's determined. She'll go like this and do the writing, but it's a lot of effort. Just a little simple thing like that where you have the types of checks that have copies to see through so she'll have to, you know, flip through them and put one elbow down and the other elbow down like this and then— and then put the elbow down, put the other one, rip it out.

Q Taking money out of her wallet?

[154] A She can't. She doesn't have a wallet anymore. She just has it loosely displayed in her purse.

Q I think you already mentioned this, changing— I'm not talking about making the bed—changing the bed. Your weekly change of the bed, stripping down the sheets, putting them back on, did she do that?

A Yeah, she's determined so she tries, but we pretty much—I—said I don't—I discourage her from doing it and she gets help with that, but she would try. And again, what's hard about changing a sheet is that, you know, when you think of the bottom sheets, it takes two hands to pull it over that corner and so what she—she just can't do that part.

Q Sewing. Diana used to like to sew?

A Yeah, I mean I could still go on with all—photography, other things like she does, but sewing is one—but yeah, sewing was one of them. She's an amazing seamstress. We got it from my mom. She's better than I am because she's more patient in general. And so we—I have many childhood and young adult—for my parents' 50th wedding anniversary, again, it was her idea—she [155] instigates all the wonderful events in our family. She, you know, everything is a party and she wants to celebrate everything so she went out without a pattern and we made these wonderful outfits. So yes, she was a wonderful seamstress, and no, she can't do that anymore. Yes, she's deeply saddened by it. She feels humiliated. I know she doesn't want to call me. She knows I'm busy, too, and she wants to protect me because I'm her little sister. She hates to call me to ask her to so something and luckily for both of us she does.

Q How about reading the newspaper, getting up in the morning, sitting in your big armchair and just reading the Times Argus, Free Press, whatever you happen to read in the morning?

A She can't do it that way anymore. She has to put it out on the kitchen table, and again, can't just sit because you have to go like this. She pretty much has to stand up to read it. She can't do it at a coffee table. She can't even really read in bed.

Q How about reading a book if she—does Diana like reading?

A She loves reading. She reads constantly.

[156] Q Good book at night, read in bed?

A No, she has trouble because, you know, again, when you're lying in bed, you have to—you know, when

you think about it, you open it up with two hands and you're reading like this and then you take your hand—you know—you take it and you hold in the middle like this to turn the page. So she would have to like put it down, turn the page or, you know, turn the page and pick it up again like that. And again, overuse. It's heavy. She basically just doesn't do it as much.

Q So she can't at the end of a long day go to bed, read a book in bed?

A Not without enormous strain and efforts and it gets her into that kind of inertia place where she's just overwhelmed. And I know like a lot of us, when we get overwhelmed, we just "Screw it."

Q She needs a table is what you're saying to read a book?

A Yes, absolutely. She can't read in bed.

Q What about unwrapping packages?

A She just rips it open, but if it's—she gets a lot—Re-Bop Records gets a lot of mail that's with that super protective tape, and again, [157] so it would involve scissors to cut the string and getting through that heavy packaging, so she basically just asks for help with that.

Q Vacuuming?

A She doesn't do it. It's just, again, the problem is that it's overuse. She has got to protect a hand that's already damaged.

Q Mopping or sweeping?

A Um, mopping really takes two hands and, you know, to put it in the bucket and then do that squeegee thing, so she gets help with that.

Q Laundry?

A Um, I've watched her take things out of a dryer, you know, a lot of us, you know, you open the dryer and put both hands in, you take them out and you put them in the basket. You know, she can do that one hand, but what she said to me this morning, she got very teary because she had borrowed some of my clothes and some of her clothes were in the laundry basket and I was just doing what I always do when I go there and kind of do a little 52 pick-up and I was taking my sweater and doing that thing you do where you take the sleeves around and fold it. And she looked at me and she had tears in her eyes. So she doesn't—she can't [158] do that. She can't fold her clothes.

Q What about folding your sheets?

A Yes.

Q Folding your linen, folding anything?

A My mother—our mother, I refer to her as a "Donna Reed" type. She—"Father Knows Best" wife, and so she has the perfect way to fold sheets and Diana last summer was determined that she wanted mom to show us how to fold sheets the right way. And, you know, I was working on it, but she just couldn't do it. I mean she can't even—so she just would, you know, again, doing the tooth thing and trying to do it. And so finally she just "I'll do it my way" and she just crumpled it up and threw it away. So no, she can't fold sheets.

Q Ironing?

A Very, very much something I don't want her doing because it's, again, that overuse syndrome of her good arm. Plus, you know, you have to take the clothes

and spread them out and usually you lay it taut and iron like this.

Q Typing?

A That was actually a skill that my father was very proud that she got in college. She's a very efficient typist, fast, and now she can only [159] henpeck. But again, she really shouldn't do it at all because of the overuse syndrome. We tried to use the voice activated typing, but they're very ineffective.

Q What about opening a jar? Opening the vitamins in the morning or a jar of aspirin at night?

A Well, you know, again, one of those things, you know, you don't think about. And even myself, I catch myself oh, whoops, sorry, I'll hand her a bottle. She'll ask me for some Excederin. I'll hand her a bottle, child protective cap, you can't do it. She can't do it. So I think the local pharmacy has special jars that they make for her, but an ordinarily going to the drug store, buying Excederin, she has to ask for help with that.

Q Does she ever call you and ask for help to open a jar or bottle?

A Yes.

Q Why don't you tell us about that?

A Well, again, that's why I mentioned the Excederin because that's the memory that I have is she had a migraine, and she doesn't get them as frequently, but when she gets them, she likes to [160] start with Excederin before the Imitrex. And so she likes to start there. And when you're in the middle of a migraine, and up—you're in chronic pain from head to toe and you can't use either arm because this one has been strained from the everyday things of the day, she'll call—she

called me up on a number of occasions, call me up and ask me "Could you please come down and just open the aspirin?" And I'll do that.

Q Let's talk about kitchen activities, going to get a paper towel.

A For her about ten come out.

Q What about cooking meals?

A Again, she's determined, and as Jessamin already mentioned, she had to get rid of most of her pots. My main concern for her is that she has a gas stove and for her to light the stove, she has to first turn on the gas, which it's an old stove so it's one of those that's heavy to turn, push it in, and turn it is strain on her left hand. And then while the gas is on, she goes over to get a match, can't do these matches, she'll grab the match from her little match box and strike, strike, strike, strike, strike, poof and, you know, goes on. Explodes at first and then—and then simmers [161] down. And same with the oven.

Q What about cutting and chopping? You need to cut an onion.

A Yeah. I've mostly—I'm trying to think—like I mostly try to see her cut meat and she'll have to ask for that—like if we go in a restaurant, she has to ask. I'll cut her meat for her. When it's just the two of us, she just picks up the steak and just gnaws on it with her fingers. Something like an onion, she just, you know, what she does is kind of props it up and tries to cut it, but it doesn't work. She—my main—one memory I have was because she loves oranges and she has to ask for help in peeling oranges and again, sometimes she doesn't like to ask so she'll peel it. But again, it's interesting to try peeling an entire orange with one hand.

Q Cooking some eggs in the morning, cracking an egg?

A She's got it down pretty well okay now, but it took practice and it still can be sloppy, but that's one of the things. And Jessamin talked about how joyous she gets when she can do the little things. She practiced and, you know, and now she can do it okay, but it's messy, and again, **[162]** it's a fine motor—it's—this adds up after the day, little things like that.

Q Buttering bread?

A Again, bread, it just—she has to make, you know, it gets all kinds of broken apart when she butters that. Toast—toast sticks, usually even that she has to put the toast down and do this and—or she'll take the butter and kind of like this, but it's hard and, again, it's the little things that add up. By the end of the day—by the end of the morning—she's really pooped.

Q Washing dishes?

A Again, a lot of strain. How she does it is she has one of those wands that have the little scrubby on the end and she'll put the pot in the sink and run the water and just scrubby, scrubby, scrubby. You know, the pan's kind of going around and so she can't really get at the grunge. She always tells me she used to judge other people for their coffee cups, you know, because they didn't get the grunge and they're gross. Now all the coffee cups have that grunge in the bottom. What other trick she does to wash cups and things is—or to dry, for example, is she will actually use **[163]** this and, you know, whoops, that's filled with water, kind of gets in there to wash, too. But it's hard.

Q Just been talking about daily activities. Haven't gotten to creative activities or athletic. So doing

all these things we've been talking about, how do they end up leaving Diana during the course of a day?

A Again, in a way I'm not used to seeing her—she's extremely—she tries so hard, and she's so determined, but she is so exhausted. And the part that I see that she, you know, the other people that see her on the streets say Diana looks so good, and she's determined, and she's a go-getter. All of that is true, but she also is deeply exhausted and in excruciating pain and just—it's overwhelmed. And then that still inertia place she gets frozen, just like with this look of panic and despair. And I'm trying and I can't do it and she's exhausted and frustrated and depressed.

Q So does Diana need assistance for doing these daily activities?

A Absolutely.

Q You've been providing that assistance?

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[165] Q Now, we were just talking about the mundane things we all do to get through the day. But recreational things, what kind of sports, if any, did Diana like?

A Um, as a family we're always into downhill skiing. We grew up with that and then moving to Vermont of course we did that together. Charlie and Diana and myself, the three of us, would go over to Stowe and she loves it.

Q Can she still downhill ski?

A She tried it once. She went over to Sugarbush to take advantage of a—

Q I'll help you out, the adaptive program?

A Yes, adaptive program and, again, that determination, she was all excited. She was going to try this and bring skiing back into her life and make sure it would continue, but she had a couple of spills and it hurt and she just decided, you know, she's got two good legs so better not—

Q Is that something you and Charlie still do every Sunday at Stowe?

A Yeah, we do and it's, you know, I feel badly we leave her behind, but I still do it. Charlie—

Q Cross-country skiing, did Diana enjoy [166] that?

A She loved it. Where we live out in Marshfield I have 55 acres of land and she has over 20 and we have gorgeous cross-country ski trails that are maintained by our neighbor and that are private and so we're really lucky and so we went out all the time, at least once, twice, three times a week. And I try to get her to go, but it's hard with cross-country skiing, you really do need the poles.

Q That's a real upper body sport, cross-country skiing?

A Yes, it is.

Q What about tennis?

A Something she always loved to do and, again, I'm seeing a big umbrella with everything she loved to do involved other people. She's a very—much more than I am—a people person and so very social, so tennis was something that she liked, skiing and cross-country skiing, tennis was something that she loved to do, plus she loved to do it with her friends, so she did it with her

friend Susan in Boston and with her husband Crow and it was a social event.

Q Can she still play?

[167] A No. No way. I mean you think, okay, got one good hand, that's all it takes, but there is no way she can do that with her overuse. Absolutely not.

Q What about just backyard games, croquet, badminton, things like that?

A We group up in Lake George so we played summer games of badminton and croquet and, again, she still tries, but I can tell because I know her, that it's that part of her that's determined and she's wincing with pain. Croquet is harder, you really do need two hands for that. You have to steady the—so we just took the—we just took it away. We have the net up, but we don't play croquet anymore.

Q I forgot to ask you about a couple of maintenance things. Just yes or no. Can she mow her own lawn?

A No.

Q She used to do that?

A Yes.

Q Shovel her driveway?

A No.

Q Shovel her walk?

A No, I do that.

[168] Q Rake her leaves?

A Not as often as I should. No, the leaves are left. She can't rake. That takes two hands and—and even if you could figure out a way to do it with your

one, which—see, I tried all these—I've tried everything with one hand. And as she puts it, it's not just one hand, it's one hand tied behind your back because, you know, the rest of us, when we try to do one hand, you have balance and she doesn't have that balance. So I tried to do that and it's just—it's hard, it's two-handed.

Q Did she used to do that stuff or was Diana the type that hired everything out?

A No, no. I mean no, she was never the gardener that I am, but she always kept her lawn mowed and raked.

Q I said I wasn't going to talk much about music because we've heard a lot about it. I wanted to ask you about—you've heard the testimony about music and the importance of it in your sister's life, correct?

A Yes, yes.

Q Heard that today?

A Yeah.

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[171] important were her hands in terms of that involvement with kids?

A Well, we saw her. I mean she was, you know, pointing with her nose and, you know, directing everybody. And, you know, we talked already about the instruments that she used which was a huge piece of it. You didn't see in that particular one, but she used that, too.

Q Liz, we've gone over this with some other witnesses so I don't want to spend a lot of time on it. After Diana got her shot of Phenergan before she went up to CVH, three or four weeks later, she actually stayed at your house that time?

A Yes.

Q Tell us what you witnessed.

A Um, while she was at my house?

Q Yes.

A Starting there? Excruciating pain like I've never seen in my life. I mean the hand itself was mottled in blue and swollen as people have said, but for her it was just excruciating pain. And the way she, you know, she's a quiet person so she'll express that pain just kind of wincing. And as Jessamin said, sounded like, you know, the groaning and moaning, but just horrible, horrible, [172] horrible, horrible, horrible, excruciating, excruciating pain. So she was given, you know, drugs to—painkillers to monitor that. And I remember once, I think it was Percocet, but I'm not sure, I remember once calling up to see how she was doing. I think I called from work and she answered the phone and she didn't know me and she—she just was in excruciating pain and had to manage it with intense amounts of painkillers. She was beside herself with pain, unmanageable pain. I don't think words—I don't think I can find words.

Q After the amputation, when Diana got home, how was it at first?

A She just was like a child coming into her home and, you know, surrounded by family, but she was just kind of walking around in a daze, but again, the part of her that everybody has shown us I think is the determined part, too. She's glad to be home and tried to make the best of it and, you know, started immediately trying to see what she could do with one hand, but spent most of the time, you know, especially, as I said, when Jessamin was around just really trying to buck up

and—but for the most part, just kind of spending a lot of time [173] trying to manage the pain and depression, you know, big depression unlike I've ever seen in her.

Q Much crying?

A Yes. Constantly.

Q By Diana?

A Yes. And by all of us, but yes, by Diana. Lots of holding each other, just crying, grieving. I mean—

Q So your strong, big sister, what kind of shape was she in?

A She was very weak and she was always, you know, again, I—she was always really strong to me and our symbol for her is Diana the huntress, which is Diana the Greek with the arrow and that was always her symbol and she has that all around her house. And now she was, you know, weak and very fragile and I had never seen that before.

Q What about her body image? How did losing her hands affect that?

A Well, they say you're as pretty as you feel and she didn't feel very pretty. So she I think felt a lot of shame and embarrassment. She assumed—sometimes wondered—but a lot of times assumed that people would be kind of uncomfortable around it, especially the children and especially [174] men. She—she just, again, confided to me as her sister that she assumed no man would ever want her ever and she still struggles with that. And then children, too, she really was worried with Re-Bop Records that working with kids, that they would be grossed out by her because kids tell you how it is. And, you know, so the stares and all that she

still gets the stares and she's very self-conscious of them. Ironically the kids have been the best.

Q You mentioned the word depression. I mean it's four years later. Have you witnessed constant depression, intermittent depression? Has it subsided? What have you seen?

A Well, I guess I have to say intermittent because she definitely is Diana and she carries her spirit wherever she goes and the essence of who she is is a go-getter and determined. She still has that huntress spirit, but it's more frequent than I've ever seen before. I would say that she is—what she is constantly is overwhelmed. Every single thing just completely overwhelms her so—so it's a mixture of overwhelmed and panic and depression weaving in and out. But the depression is always there. It's always—it's always there like peripheral vision. It's either here for her

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[176] because it's such a part of who she was. Her husband was her soulmate and her business is her heart path. John talked about that. But as her sister living next door, it terrifies me to think of her having to let go of that business completely.

Q You—Diana used to like to swim?

A Hm-hmm. Still does. Again, we grew up on Lake George and she, being older than I am, grew up on other lakes and rivers, so we've always been swimmers, all of us. We just jump off the dock and I tend to be more of a lap person, I go out and do my laps, and she likes to kind of just swim around. And first time she came out with her limb in a bathing suit, which was very hard body image for her to come out in a bathing suit.

Q This is the family's place on Lake George?

A Yes, on Lake George. Out on the dock. It took her a few days to put on a bathing suit and it took me, too, and her family to tell her she looked beautiful. And then she—once she decided to put on the suit and get out there and, again, there was that Diana part again and she went—we're all kind of like "Do we swim? What do we [177] do?" And she just went in and so we all went in and we're swimming and I'm doing my lap thing and I turn around and she was going in a circle—she didn't realize it at first because she was trying to do the crawl but, you know, doing this and so she just was, you know, going like this. And so she still swims, but it's mostly the breast stroke and she can do it, but—

Q What does that tell you about Diana?

A She's—again, she's Diana. She is—aside from my mother, the best person I know as far as goodness. Good heart. Again, she's my model. I have a lot to learn about goodness and she is my model and patience and determination, acceptance, you know. She just—she sees the good in people. She sees the jar half full and she's my model for that.

MR. KIDNEY: Thank you, Liz, I don't have anything else.

MR. O'ROURKE: We have no questions.

THE COURT: Thanks, Ms. Winn.

THE WITNESS: Thank you.

MR. RUBIN: We have our last witness for the day. We can take a five minute break or we can keep plugging along.

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[Testimony of James Rosen]

[184] that her professional life was really her self-identity. And finally, I think her lifestyle before her injury showed that she was a very well-rounded person, family oriented. She was into the outdoors, had a lot of friends, strong, romantic relationship and that she really had diverse talents and interests in life.

Q And after doing everything, Doctor, what did you—let me ask it this way, has the loss of Diana's right arm, right hand, and right forearm in May of 2000, did it cause her any psychological problems?

A Yes. She has a major depression and post-traumatic stress disorder and a body image disorder.

Q Okay. I'm going to talk about these psychological conditions, but before we do that, if you could tell us how the amputation affected Diana's functioning. And, again, we've already heard of this, but I think it's important to your evaluation so if you could just touch on it, let's start with work.

A Okay. Well, from a psychological point of view, I think as Diana tried to explain that her guitar and her music—her guitar concretely—

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[190] being very physically attractive and energetic and dynamic. And I think to the point that when you looked at her performance, you recognize that her physical appearance was—it was like a professional tool that she used in her work. And so it's not surprising that she has a lot of concerns about the changes in her appearance and how people react to her.

First on a professional level, there's a concern how are kids going to react? And she's had a lot of fears of repulsing children or scaring children or turning them

off. She has kind of conflicted ways of handling her amputation around other people. Sometimes she is sort of defensive and she'll tell the whole story about how it happened. And she'll allow somebody, maybe just an acquaintance, to see her prosthesis or her stump and sometimes she will hide herself and avoid the topic. Or worse yet, not go out and function like not going to social events or not wear clothing or something that might reveal her deformity.

Q So Doctor, your clinical conclusion after interviewing Diana and looking at all of the material provided to you is what?

A My conclusion is that Diana is an [191] intelligent person who is trying very hard to cope with her condition and she has a lot of strengths and a lot of courage, but nonetheless, despite her positive attributes, she does have depression, post-traumatic stress disorder, and a body image disorder.

Q And the tests that you conducted, the MMPI, and the interview of the standard clinical interview technique, did these support the conclusion that you've just offered?

A Yes.

Q And how so?

A For example—well, the structured interview shows that she meets the criteria for a major depression, meaning she has significant depressed moods, and I'm not talking about just the normal blues like everybody gets, but, you know, painful feelings of depression and then overly negative attitudes about herself and her future and problems in motivation and energy level. The MMPI, which allows you to compare the patients with people in general showed that she scored at the

96th percentile on depression, meaning that compared to ordinary people, only four percent of the population would score higher than her on [192] depression. So she was definitely in the clinical range in that area.

Q In terms of depression, what are her symptoms then?

A Depressed moods, most of the day—most days of the week, loss of motivation, some problems with weight maintenance. There was a time when she slumped into a deep depression and lost too much weight and her prosthesis didn't fit her; problems in concentrating and making decisions. There was a time when she had death wishes. Those kind of classic symptoms of depression.

Q Doctor, could you just in everyday terms, like you were talking at the kitchen table, tell us what it means—what does it actually mean when you suffer a major depression?

A Well, I think one way would describe it is that it's a feeling that really hurts, you know, that you feel sick to your stomach inside, achy, hurty. And then there's the whole attitude that goes along with it, which is that things seem so bleak that you can't imagine things better and that whatever bad is happening to you now is so bad that life, you know, might not be worth living.

Q What about antidepressants? Diana is on

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[203] surprising. You could predict that her depression would continue and maybe even get worse.

Q So Doctor, do you consider Diana's psychological conditions with respect to depression, post-traumatic stress disorder, and the body image disorder,

do you consider these to be permanent or will they be resolved sometime in the future?

A Well, I don't see them being resolved anytime soon. These are problems that are going to continue and that's largely because the stresses that cause these kinds of problems aren't going away. She'll forever have to face her disability and the impact on her lifestyle and career and relationships. Those aren't disappearing, so she's always going to have some ups and downs in her mental health. Her post-traumatic stress disorder, you know, although she might be bothered less by it at some times, will not go away because, you know, she's not going to forget what happened to her and she has this constant reminder. So these are persistent problems that she'll have to learn to deal with.

Q Permanent?

A Yes.

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MARCH 10, 2004

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[Testimony of Dr. Mark J. Bucksbaum]

[33] Phenegran intravenously.

Q I'm going to interrupt you because what I would really like to do is start with Dartmouth because I think we've heard this several times.

A Okay. It came to be that as the necrosis of the hand or the injury to the hand progressively worsened, that they decided that the limb was—the survival of the limb was threatened, and at that point she was transferred to a higher level facility, which was the Dartmouth facility, to try to address saving of the limb.

Q What was going on with her hand medically—physically?

A At that point the hand was becoming necrotic, it was pre-gangrenous.

Q Let's stop there. Necrotic?

A It was dying. The tissue itself was turning—was initially red and it goes through a transition where it ultimately becomes black and there are transitions of colors between that, but it's—essentially the limb is 'failing to survive. It's not getting the nutrition that it needs and the tissue starts dying off.

Q Gangrenous?

A Yes.

[34] Q What is that?

A That's the next stage after the necrosis. It's when the tissue starts to literally break down and there becomes liquidification of the tissue. If it's left unchecked, becomes a life threatening event where it can progress further up the limb. The prospectus is to try to save as much of the limb as possible. This is looked at first through a viability of the tissue and there has to be a clear margin of tissue where we believe that the limb will survive or what's left will survive.

Once that's determined, the next consideration is how many joints can be saved? Each joint in our body represents function or more function if we save it. So decisions are made to try to preserve as much function as possible by saving as many joints as possible. In this case the initial attempt was to try to save the wrist, and that was the first procedure that was performed was an amputation to spare the wrist. And unfortunately, over the next several days the condition wors-

ened and it was felt that they needed to go and do a revision where they had to go above the wrist. At that point sparing the elbow was the major concern. And then the other consideration is [35] having the optimal leverage to assist using an artificial limb. Too long is not good, it creates a problem. Too short creates the same problem the other direction. So there is an optimal distance that we would like to have when we're making those selections.

And that's what was considered in her case, where she ultimately went on to have an above the wrist or below the elbow amputation.

Q Was she at risk of death?

A Yes. As I mentioned, it's a fairly serious situation. The tissue is dying, the vascular supply to the area has been compromised.

Q Vascular supply?

A The arteries and the veins have been compromised. Because of that one of the medications that she was given were blood thinners. The reason for the blood thinners is to prevent clotting or further worsening, but if an individual gets a clot, that clot can then move up through the arteries and it can create quite a bit of problem for the lungs and for the brain. And it is an extremely serious risk for which they did take it seriously and tried to medicate her to prevent that. That's also—part of the decision in going [36] to an amputation is to sort of minimize the potential damage or the long term risk.

Q So the amputation in a sense is to prevent a risk of further damage or death?

A That's right.

MR. RUBIN: Your Honor, there are five photographs of the hand that I mentioned to the jury. I'm going to start—and they've been admitted by agreement previously. Could we see Exhibit 41 please?

THE COURT: All right, so 41 is admitted by agreement.

MR. O'ROURKE: Yes, your Honor.

THE COURT: Just so we get it all out of the way, what are the other numbers?

MR. RUBIN: By agreement 41, 27, 28, 39. And what do you have in front of you? There is a number on the back.

A Forty.

MR. O'ROURKE: We have no objection, your Honor.

THE COURT: Twenty-seven, 28, 39, 41, and 40 are all photos and are all admitted.

A The first thing we notice is the markedly swollen limb, which is the body's healing [37] response.

Q Let me just put the time frame on this. This is April 30th?

A Yes.

Q And I think she went to Dartmouth the 26th of April, so this would be four days after admission?

A So what we're seeing is the redness, the marked swelling. There is a—what we call a demarcation line. There is a essentially a margin that you can see through here. The physicians have put some dots there. I think you can see from here, showing where the current line is. Essentially we're doing this so we

can monitor the progression of this. This hand is in considerable jeopardy. As you can see, it's a very deep, dark purple color. The fingers are markedly swollen. In this view we can't see the fingertips, but the hand is becoming necrotic, which is a process that starts down at the tips and is going to—as we can see further on—move up the limb as we go.

Q Let's have the next picture.

A This is another view. We can see again the demarcation lines. The fingers, again, are markedly swollen, deep purple. Here we can see the [38] nails are black and we can see that the blackness is extending up into the tissues of the fingers. And this is an ominous sign for the hand. At this point they're still aggressively working with medication management in terms of limb salvage.

Q You had talked—you're an expert in pain management?

A Yes.

Q Obviously this hurts, but can you describe the level of pain that's associated with this kind of condition?

A Um, this is one of the examples that we use when we establish a pain scale. Pain scales are usually run from one to ten. This is a ten and it is extremely painful. There is a chemical reaction that's going on in the hand that will essentially put the nerve endings on fire and there's not much worse than this type of scenario.

Q Next one.

A What we can see now is that first these were the original dots that we had talked about. This has

progressed quite a bit up into the hand. This discoloration that you see now is markedly necrotic tissue. This —essentially this hand is pretty much at jeopardy. It's extremely unlikely [39] from this stage that this is going to turn around with just medications. And you can see that this now—that really dark, almost black in color is progressing up into the upper part of the hand. The demarcation line is a couple of inches higher than where we had previously seen.

Another view showing the same thing. The extension above the wrist again is a very ominous thing for us. You can see the darkening of the skin. While there's some viable tissue in here, all of this on the outside of the hand and the thumb are really nonviable at this point.

Q What about—seems to be moving up into the forearm?

A Right. And that's what I was saying. Once we —remember, we're talking about preserving function by joint levels. So once we've moved across the wrist, this is already a very poor sign for us. And at this point the surgeons are clearly concerned whether or not they will be able to save a wrist or not since it's already jumped over.

Q The fingers seem flat. Have they lost their fullness there?

A They have. This is part of that process where I was talking about where the tissues [40] actually are liquifying. They're losing the muscle mass and supporting structures. The bone is dying off and so in this view we can see the distance from here to here is very narrow. That's the side of her finger. She's lost a tremen-

dous amount of volume, which again, is essentially an unrecoverable point for the hand.

Q Let's turn that off. Thank you. Go back. We heard quite a bit from Diana's sister yesterday about loss of function on a daily basis, but I would like you to talk about it as a professional about the impact of the loss of her arm on the activities of daily living.

A Um, it's a major loss in function, as I'm sure you can all imagine. But simple things such as like buttoning a sleeve become impossible without having both hands. It's extremely difficult for her to do basic dressing, just putting on clothes, belts, socks. These are the everyday sort of things that we have to do. Just tucking her shirt in often requires both hands as an assist. Even for her to put on her prosthesis is a real problem because she doesn't have two hands to manipulate the device.

So even though it's a device that could [41] potentially help her, it's an effort in and out of it and we'll perhaps go over that some more later. Just basic personal care, brushing your teeth, combing your hair, hooking your bra, all of those kinds of functions are markedly impaired by it. I think one of the biggest issues for her was that she was a professional musician and needed to have both hands to play her guitar. And so the loss of the limb essentially took that task completely off line and now she's being slowly retrained how to sort of reapproach that. But it's—it's heavily impaired for her to do that.

She liked to work with clay; obviously that's a bimanual task and extremely difficult to do when you're one-handed and not particularly supported through adaptive equipment such as prosthetics.

Just basic things, cooking; you can all imagine the various cooking tasks, stirring, mixing, pouring. It all becomes a big problem for her, one in which she has to rely on her remaining limb to do, which is—it's quite difficult.

Q Let's talk about pain, and it may also relate to functionality here in this conversation. Does she have pain today and subsequent to her [42] release from the hospital as a result of the amputation?

A Yes. A fair amount of it.

Q Let's talk about her phantom pain or phantom hand first.

A There are two different pains, three if you're allowing for emotional pain. But there's the physical pain, which is the pain that you perceive right at the tissue. When I showed you the hand and we saw the fingers dissolving, in essence that's the immediate physical pain that's there. There is another type of pain that happens in loss of limb, which is called phantom pain. Phantom pain is a disharmony between your brain's model of your body, your body's image of itself, and what's really there. So that your brain still thinks you have a full hand, your reality is it's gone. If you close your eyes, you can still see your hand there. You can even feel the fingers moving. That's not painful. That's phantom sensation, but when it becomes painful, there's literally an electric or burning type pain in the fingers, in the part of the hand that are no longer there, but it's on fire and it's extremely painful and it travels up the arm to the brain.

[43] The body has not adjusted to the loss of the limb. Even though those nerves are not there, the pain is incredibly intense and extremely difficult to treat.

Q Diana has described some feelings of—in addition to that—some numbness and tingling feelings in the hand that's not there.

A That's already good. That is—sort of an in-between stage when some of that burning and pain is starting to calm down a little bit. You're still left with this electric like feeling, with a numbness. It's extremely distracting at best, if not completely painful.

Q Does she have any problems with her upper body, her back, neck, musculature as a result of this?

A Yes.

Q Did she have any problems with her back, neck, muscle pain before this that you were able to determine?

A Not that I'm aware of.

Q Okay.

A First and foremost, energy of our walking is combination of the whole body event, including swinging of the arms. We conserve energy [44] by using the arms in a pendulum fashion which brings momentum to the upper body and helps propel us forward. When you lose a limb or part of a limb, you've disturbed some of that momentum. So just on the most basic level, it costs her more energy to go across this room than it would have had the limb still have been there.

There's other issues which is just the weighting factor of the limb, the balance that the limb brings to us that you lose. And when you don't have it available, other muscles have to come into play to make up the difference. Ultimately that creates a strain pattern and an overutilization, which transmits some of those forces to the other side of the body and the body will do its

best to accommodate that. But at a certain point, if it becomes unable to cope with it, it is an overwhelming of it and we end up with new medical problems in these areas as compensation.

Q Problems like what?

A Well, particularly you can have strain across the neck and you can develop strain and tendonitis patterns, which is exactly what she ended up doing.

[45] Q Does she have a problem with tendonitis in her remaining hand and arm?

A Yes.

Q And how serious is this?

A Well, it's quite serious. There's been flare-ups of it as time goes on. When it gets severe enough, it brings her only remaining limb off line because at that point it needs to be rested. One of the—

Q What does that mean off line, needs to be rested?

A She can't use it. And so when—you'll see later with her life care plan, there were separate tracks in that plan, but one track is to consider what happens when she can't use her remaining arm when it is flared up. It's prone to flaring up because it's being greatly overutilized since she doesn't have the original limb. The problem is that the courses of treatment for—

Q I need you to talk a little more about what actually is going on in the arm that's causing the pain. What is the tendonitis exactly?

A Well, tendonitis is initially set up by a strain, overstressing of the muscles and tendons in the limb. And that is happening because she has [46] to compen-

sate for the loss of the other limb. If it's taken too far, the body produces an inflammatory response, which then becomes the "itis" in the tendonitis, which is the inflammation of the tendons. That in its own right is very painful. Can become chronic. One of the mainstay treatments is to inject it—which you can imagine would bring tremendous concern to her. So that's not a treatment that we can use for her. And primarily the mainstay treatment for her is to rest the limb and let it calm down.

Unfortunately, we're heavily dependent in the plan that she could use that limb to do certain things for herself. When medically she's told not to use the limb, she looks like a bilateral amputee because we've taken away both arm functions at that point and it leaves her a hundred percent dependent on other individuals or she has taken to using her teeth as a way of holding, which is not necessarily a desirable thing to do, but it's out of desperation. If you can't hold it with your hand, then you hold it with your mouth. This has its own problems.

Q Does she have to limit what she does with her good hand to avoid disabling herself?

[47] A Yes. Repetitive use of the remaining limb is going to aggravate this sort of underlining lingering tendonitis. Tendonitis has never really gone away. Its intensity changes based on her activities and also tends to fluctuate with weather so she has to preserve it as much as possible, which means that you have to kind of pick and choose your battles. Where are you going to push the limits a little bit and the rest of the time rely on devices or people or other parts of your body to make up for it?

Q We've heard from Dr. Rosen, the psychologist, who evaluated her. Did you review his report?

A I have.

Q I'm going to ask you some questions about how all of these conditions affect her ability to work. Is that something that you do as part of your profession?

A Yes.

Q What are you doing when you try to assess someone's work capacity?

A Well, the bottom line is are their injuries compatible with their original work? And—or any work? And then to make some

* * *

[51] A Just give me one second to turn to the report.

Q He testified he did an MMPI and showed her in the 96th percentile.

A Yeah, which is very severe. Just looking for the actual numbers. Just give me one second. In the scale that we use, which is moderate to marked was the level that she came out, which is the second from the highest.

Q That's on your own evaluation?

A That's correct.

Q So it is your opinion that she does not have the capacity to hold a full-time job?

A Yes.

Q And what about a part-time job?

A It's very limited to what she can do. The—in particular, she has tried to work with the guitar and tried to reintroduce this. It's really not gainful. The

amount of time, the lack of precision, it's stifled at best to the artistic process, but just from a mechanical process, it's so fatiguing and draining on her that after a couple of hours, she's really too tired to continue.

The medications also play a role in that.

* * *

[Testimony of Myron Smith]

[110] Q What is your assessment of her ability to obtain gainful employment?

A My opinion is that Diana does not have the capacity to engage in gainful employment.

Q Full-time employment first.

A She absolutely does not have the capacity to engage in full time employment.

Q Why not?

A All of the resources that we discussed, psychological, the medical, the vocational evaluation by Easter Seals, the functional capacity data, all indicates that she has number one, a less than sedentary physical capacity, and she doesn't have the capacity to sustain work activity productively, work activity for substantial periods of time. Now, plus at age 55 or older the Social Security Administration, who's been at this for decades, defines us as persons of advanced age. When we reach that age category, our transferable skills, those skills that we've acquired in past work need to be directly transferrable to a new job. We aren't very successful in teaching older folks to do new things when they have the addition of a handicapping condition. We just simply aren't. **[111]** So when I took a look at the 72 worker characteristics that the federal government defines every single job in the United States economy

practically with these 72 worker characteristics, we looked at Diana's prior work history. What is it that she did? We looked at what are her residual capacities? And we tried to match these up. And as wide of analysis as I did, no jobs were identified in either the Vermont or national economy for which she had the residual capacity to perform.

Q Forty hours a week?

A For 40 hours a week. For one hour a week. She had no transferable skills that would meet the worker characteristics of existing jobs. Now, that doesn't mean she's unemployable. What it means is one would need to find what we call a benevolent employer who would be willing to allow her to work on her schedule, probably two to three hours a day every other day, take time off for medical appointments, missed time due to medical conditions, exacerbation of the other arm and bring to the work site a very limited skill base. So to that extent those employers for the most part don't exist and they certainly don't exist when you're 55

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[Testimony of Allan Stuart McCausland]

[143] present value using the one and a quarter percent the same way. We then sum up the present value. And so relative to the arms, we have a present value cost of $372,287. That's the amount that has to be set aside today in order to cover these expenses.

That exact same methodology showing you in those two was done for each one of these categories within the life care plan, each item that's—the 372, there is the 103. I did it for each one of these items and we end up with a present value cost of the life care plan, to provide for the needs of the life care plan of $1,280,266.

Q Do you have a summary?

A This is a summary of all of the present value of the economic loss, 725,532, and the present value of the life care plan costs of $1,280,266, and then we end up with a total present value for the cost and the economic loss of $2,005,798.

Q Do you believe that these numbers are correct to a reasonable degree of economic certainty?

A Yes, I do. I don't have any reason to doubt them at all.

* * *

[Testimony of Diana Levine]

[163] pretty much out of my mind with pain. And completely disoriented and just about as bad as a migraine can get.

Q And where did they ask you—or put you?

A They took me into a room and they are very familiar with my situation when it gets that bad, how to treat me and, you know, I have a cold cloth and I have something to throw up in and I have the lights dimmed because I'm very sound and light sensitive and—

Q Did Jessica tell you she was going to give you some intravenous medication?

A Yes.

Q Do you know how long it took her to administer the medication?

A Not really. I—I was so out of it I don't have a strong memory of that.

Q Who would be in the best position to know how long it took?

A She would.

Q If she said it was more than two minutes, do you have any reason to doubt that?

A No.

Q At some point did you feel some severe [164] pain?

A Yes.

Q Do you know how long before you felt the pain that she had been administering the medication? In other words, did it happen right at the beginning or along the way? Do you have any idea?

A No, I mean listening to the testimony and seeing the tubes and everything, I realize there's a whole big process to it. And I was so out of it, I really had no consciousness of that, like when it happened, because I was like this—with the head covered with the rag anyway. But I know that it hurt.

Q Now, were you asked at one of these depositions to repeat or say what you said when it hurt. Someone asked you to actually speak as you remember speaking then?

A Yes, yes.

Q Why don't you do that here and tell—just kind of the best you can tell us what you said in that examining room when you felt that pain.

A "Ow, that really hurt."

Q And it did really hurt, right?

A (Witness nods.)

[165] Q Did it continue to hurt?

A Yes.

Q Did you say anything after that initial statement?

A No, because I knew that it was going to end.

Q In other words, she said "Hang on, it's going to be over"?

A Yes, yes.

Q The next six weeks, we've heard from your sister and your daughter and Steve McArthur about that experience, and I don't want to belabor it, but how would you characterize the three or four weeks before you went to Dartmouth and the five weeks—I guess more than six weeks—five weeks you were at Dartmouth?

A From when it happened to through when I was at Dartmouth?

Q Yeah.

A Um, it was progressively the most excruciating pain I've ever been in. I've never experienced anything like that and hope I never have to again. Friends of mine said they didn't—by the end of it, didn't even recognize me and evidently I didn't recognize them and that's how **[166]** out of it I was between the pain and the morphine. And I was terrified. I guess that would characterize it, just like in horrible pain and terrified.

Q How long were you terrified?

A I was terrified the whole time but I was just doing everything I was told and feeling like I was going to be okay. But when I got to Dartmouth I think is when it really became clear to me that this was a life or death situation.

Q And you went through two amputations?

A Yes.

Q Since your discharge from Dartmouth have you suffered any pain as a result of the amputation on an ongoing basis?

A Yes.

Q All right. We've heard something about the phantom pain. Why don't you tell us about that first.

A Okay. I've become an expert on phantom pain. What it is is you feel like you have a hand, even if this is off, and I'm looking at my cut off limb, I still feel like I have a hand. My brain just doesn't get it. It's a huge hand like a Mickey Mouse hand and the fingers only go about

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[200] Q Yes, page 117. It starts at the bottom on line 25 and it goes over—

A "After she asked me—after she told me about giving it IV would work more quickly"—after that?

Q Let me get it for you.

A Okay. Okay. "What did Jessica say to you regarding this treatment after she answered your question that by giving it IV it would work more quickly or words to that effect?"

Q And your answer was?

A "Okay, the next thing she said was after I"—oh, wait a second. After I—something's missing here.

Q Does it say "After I screamed"—

A No, I don't—oh, okay, you go up there. "She said—the next thing she said was after I screamed, when I said—when I yelled 'that really hurt' what Jes-

sica said is something to the effect of 'it's supposed to burn. This medicine burns. You need to hold still so you don't disturb the needle.' So I held still."

Q And that was the fact of the matter as you recited it back in May of 2001?

A These are the words that I said. I know [201]—like I demonstrated earlier—that I didn't scream and it looks like I corrected myself here. When I screamed, I said when I yelled, that was my version of a yell, which is probably even more than what it was because when I have a migraine a yell is really a yell from inside my head because I'm in so much pain and I'm sound sensitive. So if what I said earlier when I said "Ow, that really hurts," if that constitutes a yell, then that's what it was.

Q Was it also one of the most intense pains that you had ever felt?

A Um, to that point, yeah.

Q And look at—did you say in that deposition—look at page 121 on line 22.

A 121, 22? Yes.

Q It was like your arm was going to explode in pain?

A Yes.

Q And when you did tell Jessica, you said it in an elevated voice, did you not?

A Yes, the way I said it earlier.

Q And if you look on line 16 of page 121—I'm going to try to stay right with the same deposition if I could. Did you tell the examiner [202] that it was "one

of the most extreme pains I've ever felt"? Isn't that right?

A On line 21?

Q Line 16.

A Line 16, yes.

Q It says, "It was one of the most extreme pains I've ever felt"?

A Yes

Q Now, on page 121 did the examiner also ask you as to what area of your arm felt the pain? From where to where? And look at page—at line 23.

A Okay.

Q Is that the question that the examiner asked you, what area?

A Yes.

Q And on line 25 what did you tell him?

A "Definitely my forearm. I don't remember it being up here."

Q So it was from your elbow down, was it?

A Yeah, I just remember it—

Q The pain—

A Yeah.

Q —was from the elbow down. And if you look at page 122 on line two, did you tell the [203] examiner that it was nothing above the elbow, that the pain was below the elbow and down?

A I said that—as far as I remember I said "I don't remember anything above the elbow, but this is the memory, the lower arm from here down."

Q And the examiner asked you if you felt any discomfort in your fingers on line five there at page 122?

A Yeah.

Q What did you tell him?

A I said that "I didn't isolate it." That it was just from here down, which would include the fingers.

Q Then when I was asking you some questions, and I had the benefit of this deposition, you remember when you were there?

A Yeah.

Q But we'll go to the questions that I asked you now so we won't get mixed up, and that's the deposition that was taken about 30 months later. It was taken November 13th or November 23rd?

A Thirteenth.

Q November 13th, 2002 at Mr. Rubin's [204] office. Go to page 33 of that deposition if you could to line six.

A Okay.

Q And I asked you just above that, "What happened, if anything, during the time that Jessica was infusing the medication into your anatomy" And on line six what did you tell me?

A I said "That's when I—that's when extreme pain occurred."

Q And I asked you then on line eight, "And did you raise your voice and tell Jessica that it hurt and it

was a burning sensation?" And what did you tell me when I asked you that question?

A I said, "I didn't say it was burning. I said "Ow, that really hurts.'"

Q And I said "What did she say?" And what did you tell me? Line 13.

A "She said—these aren't the exact words, but something to the effect of 'It's the medicine. It's supposed to burn, so just hold still so you don't disturb the needle.' That's my memory of what she said."

Q And then I asked you whether or not—on line 18—"At any point when you said that it was burning, it was hurting, did she stop infusing [205] it into you?" And what did you tell me as to what she did, whether she stopped infusing or not?

A I said that "It didn't—I didn't get the sense—I didn't get the sense that she stopped infusing me. But what I remember is that when she told me to be still, I held still. And it didn't seem like it lasted that long so I was relieved about that."

Q And then I went on and said, "It didn't seem it lasted that long. You mean her infusing the medication into your system? Into your anatomy?" And what did you say?

A "Yeah."

Q And I asked you on line four, "Can you tell me how long you think it took for her to do that? From the time she started until she ended?" And what did you tell me?

A I said, "It seemed like maybe a minute or so. Again, it's hard to really—'cause my perceptions were so influenced by the amount of pain I was in."

Q And then I followed that up by saying, "All right, but a minute is your best judgment to date?" And what was your answer?

A I answered "Yes."

* * *

[208] Redirect Examination by Mr. Rubin

Q Let's go back to—got your pages all over the place.

A It's just like home.

Q See if I can help you here.

A Yes.

Q We want to find page 118 wherever that is.

A Okay. Of K or L?

Q K. It's got four boxes on a page, your Honor.

THE COURT: Yeah, it's the scrunch thing.

Q Here it is. Now, what I want to do here is start on page 117 at the bottom and we're going to go right through the whole—the whole section of that answer, okay? Mr. O'Rourke asked you a question starting—I'll read the question and you read the answer, okay?

A (Witness nods.)

Q Go through the whole thing this time.

MR. O'ROURKE: What line are you on?

MR. RUBIN: I'm sorry, page 117, line 21.

Q Question, "What did Jessica Fisch say to you regarding this treatment after she answered your question that by giving it IV it would work [209] more quickly or words to that effect?"

A "She said—the next thing she said was after I screamed—when I said—when I yelled 'that really hurts' what Jessica said is something to the effect of 'It's supposed to burn. This medicine burns. You need to hold still so you don't disturb the needle.' So I held still."

Q Question, "After answering your question about why she was going to give you medication IV she didn't say anything at all you remember until you remember yelling out or saying that something hurt and then she made a response to that remark that you made?"

A "Yes, she reassured me."

Q Question, "Now, when you say you felt something and yelled 'It hurts,' I have in my mind's eye of somebody yelling. Did you literally yell so that somebody standing out in the hallway would hear you? Or did you just in a voice say 'Jessica, that hurts' in a speaking voice, but not literally yelling? I'm trying to understand just what occurred."

Now, when that question was asked, did you attempt to say exactly in the same tone of voice?

[210] A (Witness nods.)

Q What did you say?

A "Ow, that really hurts."

Q Question, "Now, what you said was clearly in an elevated voice above a speaking voice." Answer?

A "Yes."

Q Did you scream?

A No.

Q You were trying to remember what happened in this situation at this time a year after or 13 months after it all happened?

A Yes.

Q Do you really remember at what point during this injection the burning or the pain started?

A No. I was in horrible pain and anything would be guesswork.

MR. RUBIN: Thank you.

Recross-Examination by Mr. O'Rourke

Q But when you answered those questions to the other examiner, you agreed you were under oath and you were recalling it as best you could?

A Yes.

Q The same as when you answered my

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MARCH 11, 2004

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[Testimony of Dr. Thomas Garvey III]

[85] should be used. Is that an instruction to physicians?

A. Certainly.

Q. The next sentence says, "When administering Phenergan intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily." What does that mean; is that an instruction to physicians?

MR. RUBIN: Objection, same basis. He's testifying about what an infusion set known to be functioning properly is a technical question.

THE COURT: I'll allow it. I think what we'd like to hear, Doctor, is what do these words mean, because they're not familiar to all of us.

A. Okay. First, let's—get to an infusion set. Usually an intravenous infusion set comes in a sterile sealed package and consists of tubing and connectors, and as well as it may have a cannula in it. It's usually an intravenous infusion set is usually used to connect a needle or a cannula in a vein, sometimes in [86] an artery, not in this case, in a vein to a source of intravenous fluid, either a pump or a hanging bag, so the set is a set of tubing. There are other ways to give IVs, as we all know, and it says here it says that it's usually preferable to inject this drug through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In this case you're in a vein, you get blood return, and you can put some saline in there and it flows freely, so pretty much you're in a vein, but it says "preferable," it doesn't say you always have to do, because, as you know, there are other situations you want to give a direct intravenous injection of Phenergan and other drugs, but it says that it's preferable. The downsides are time involved, lower concentrations achieved, and there are various other problems. Direct intravenous is quick, high concentration, with a bolus you get a shot of it.

Q. Okay. Then says "In the event that a patient complains of pain during intended intravenous injection of Phenergan Injection, the

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[103] Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set."

Q. And language close to this was put into the labeling for Phenergan?

A. Yes.

Q. So does this indicate that this language was provided by this Advisory Committee of experts?

A. Seems to be.

Q. Okay. While you were at FDA, were you aware of a program that the FDA initiated to change the formatting of labeling in the late '70s?

A. Yes.

Q. Can you describe that briefly to the jury?

A. Well, there were a lot of drugs on the market with labels that were very old and did not have uniform formats. Now, most of the drugs I dealt with, we already had draft guidelines for what the format should look like, and it was decided that the Agency should make happen that all of these old drugs with the old labels and funny formats, not necessarily funny formats, old formats should be redacted, in those cases the labels should be [104] redacted into the modern format, and they issued a so-called Federal Register notice instructing the firms that had such drugs to do so.

Q. Did Wyeth make a submission under this program for the Phenergan label?

A. Yes.

Q. And when was that submission made, if you know?

A. I think it was in '81.

Q. Okay. Let me go ahead and mark a document. I think you've got it, right?

A. The Federal Register notice requests having been made in '79 and amended. I—again, I think in '81, so the duration is not too unusual for this kind of thing.

MR. RUBIN: I'm sorry. I haven't seen this. It's eighteen pages.

THE COURT: All right. We've been at it for over an hour. We'll take a break, give you a minute to look it over, give everybody a chance to stretch.

(Court was in recess from 11:05 a.m. until 11:20 a.m.)

BY MR. HOFFMAN:

* * *

[128] well qualified. I think he was a full professor at the University of West Virginia in Morgantown which are disproportionately—not fair thing to say. Good medical center and is a balanced intelligent person.

Q. How long has he been at the FDA?

A. Oh, dear. I don't really know, fifteen, eighteen years, perhaps.

Q. And what's his current position at FDA?

A. He's the Director of the—of—of New Drugs.

Q. What does that mean?

A. He supervises all these new drug applications, neuro, pharmacologic, cardiac, renal, so forth and so on.

Q. The letter that we talked about, the February '97 letter, do you think that reflects an administrative error on the part of the FDA?

A. No.

Q. Okay. I want to mark, or, actually, I know it got marked into evidence. I was going to show you, this is defense Exhibit N. Is this Wyeth's response to the February '97 letter?

A. Yes.

Q. Okay. And does it provide the attached final

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[135] Q. I'm going to read you something from—I'll ask a preliminary question. When there would be meetings between drug companies and representatives of the FDA, was it common that the people from the FDA and the people from the drug company would decide that they would keep the minutes of the meetings secret so there would be no public access to those?

A. Well, there is certainly—excuse me. There's certain situations where they're secret. FDA is proprietary and meetings regarding a new drug application are generally considered, if you will, secret or confidential.

Q. Read—I'm going to read you a section of the Exhibit 17, and you remember who Dr. Clark was in this memorandum?

A. Yes.

Q. And that was a representative of the FDA?

A. Yes.

Q. Dr. Clark then commented that, "If we exchanged minutes, these would be subject to public availability under the FOI," Freedom of Information Act?

A. Yes.

* * *

[152] the vein, yeah, that's possible, sure.

Q. Let me try it again.

A. Sure, you want to try it again, we can try it again.

Q. You know the method by which this drug was administered?

A. In this case?

Q. Yes, the assume—let's assume the method we talked about was the method used in this case for purposes of this question. Would you like me to state that method again?

A. Yes.

Q. Take two Tubexes, each with 1 cc, you transfer those into a 3-cc syringe. This is a 3-cc syringe?

A. I'm familiar with them.

Q. You attach that 3-cc syringe to a butterfly infusion set. You're familiar with that device?

A. Yes, very much so.

Q. And then you administer the medication through this butterfly infusion set at a rate of 25 milligrams per minute, making sure that the fluid is flowing?

A. And your question is?

[153] Q. Is that consistent with the label?

A. I think it's consistent with the label, although I wonder why one would bother.

Q. You've answered my question. And it is foreseeable that a clinician would administer it the way it was administered to Diana Levine?

A. Now, you must remind me how it was administered to Diana Levine.

Q. Take 2 cc—two Tubexes, you transfer into that syringe, you attach it to the butterfly, and you push it slowly into the arm?

A. That wasn't my impression with respect to how it was delivered.

Q. It's not your understanding that 2 cc of Phenergan were transferred into a Tubex—into a 3-cc syringe, attached to a butterfly, and then administered into Diana Levine's arm?

A. My—

Q. You can answer that "yes" or "no." If it's not your understanding, that's fine.

A. That this was through a flowing system, no, I didn't remember knowing that was through a flowing system.

* * *

[168] system?

A. I'm not—is that the same question you asked me.

Q. Yes, it is.

A. I think my answer's the same.

Q. So you would not want to ensure that?

A. No, I would not want to preclude other methods of administration.

Q. So you would not want to ensure that it was done only through a free flowing established or piggyback system, correct?

A. Yes, that's correct.

MR. RUBIN: Can we have slide number on page 74.

MS. DeWOLFE: Begins, actually, on the bottom of page 73; is that correct?

Q. One second. Yes, it begins at the bottom of page 73, line 24. Question: "So given the high risk associated with extravasation or intra-arterial injection, I think what you're telling me is you would want, as a consultant, the label to ensure that the medication was piggybacked through an established IV?"

Answer: "The label unfortunately can't [169] ensure, that it can recommend."

Question: "The answer is, though, that you would want to write the label to instruct that; is that correct?"

Answer: "Yes."

A. Yeah, not exclusively sure.

Q. There's no question, Dr. Garvey.

A. Oh, I see.

Q. You are more than just a consultant; you also treat patients, as you said?

A. Well, I treat patients, yes.

Q. It was not a trick question. You are also a treating physician?

A. Yes.

Q. And you're concerned, obviously, about the welfare of your patient, right?

A. Patients, yes.

Q. And knowing what you now know, in a non-life-threatening situation, if the only benefit was to enhance

the speed of action, you would hesitate to use a butterfly system to administer this drug?

A. I think I would.

Q. One thing I noted that, when you testified earlier this morning, you said at some point

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[172] Q. Okay. You were asked if you would be hesitant to use a butterfly infusion set with Phenergan, do you recall that testimony?

A. Yes, just a moment.

Q. Does that mean that the use of that should be prohibited in all circumstances, use of a butterfly?

A. No. I think one needs to think a lot about it. There are some times when the only venous access is via small bore needle, for instance, with the butterfly sometimes you can't get in otherwise.

Q. You were asked about risk/benefit calculus. You're a gastroenterologist?

A. Yes.

Q. Do you treat patients who are extremely nauseous?

A. Nauseated, yes.

Q. Patients who are vomiting heavily?

A. Sure.

Q. What are some of the risks associated with heavy vomiting?

A. Dehydration, electrolyte imbalance, constipation, hypotension, arrhythmia.

Q. Were you done with your answer?

[173] A. I think I must have been, yes.

Q. And you know those risks as a gastroenterologist?

A. Even just as a regular old internist.

Q. Are there situations where a patient having that problem at risk for some of the serious consequences that you just described would need immediate relief?

A. Yes.

Q. So there is a class of patients for whom IV used through a butterfly is appropriate?

MR. RUBIN: Objection.

A. Yes, theoretically.

MR. RUBIN: Leading him through the way what he wants him to say, but it's a leading question.

THE COURT: I'll sustain the objection.

MR. HOFFMAN: I'll rephrase, Judge.

THE COURT: Thank you.

Q. Any patients that you can conceive of for use of a butterfly set would be appropriate?

A. Using a butterfly?

Q. Yes?

A. And direct injection?

[174] Q. Yes?

A. Somebody who has been vomiting to the point of severe hypobulimia, fluid depletion, veins are very tough to get into. You may be only able to get in with a butterfly. If they're vomiting, you want to get in right away, get in, give the drug. There are situations. I think the Agency was thinking about that.

Q. You were asked about a question and answer on page 128 of your deposition. I believe it was started on page 129, when you were asked, but I want you to go to two pages before, 127, line 25. I'll read you the questions, you read the answers, okay?

A. Okay.

Q. Question: "Well, I'm asking you to make an assumption. I don't know whether you have or not, let's just make an assumption—forget that. How many have you seen?"

Answer: "I think that among the 3500 as I think at last tally there was 32, I would have to recount, but I think it was 32."

And I'll stop here., Were you referring to adverse event reports here?

A. Yeah, I think so.

[175] Q. Next question: "How many of those involved some form of amputation?

Answer: "I haven't tallied them, I haven't had a chance to do this, but a substantial number."

So, when you told Mr. Rubin you meant a substantial proportion, you really needed to hear that question before to understand what you were saying?

A. Yes.

Q. In fairness?

A. Yes.

Q. All right. I have nothing further.

RECROSS-EXAMINATION BY MR. RUBIN:

Q. So of the 3200 or so adverse product events, adverse events that you reviewed, a substantial portion of or almost close to 32 of them were amputations?

A. No. I think that there were 32 amputations—32 intra-arterial injections or perhaps extravasations. Among them a substantial proportion involved amputation so some fraction of 32, not a small fraction.

MR. RUBIN: A substantial one. Thank you.

[176] MR. HOFFMAN: One question.

RE-REDIRECT EXAMINATION BY MR. HOFFMAN:

Q. I think you stated earlier you estimated it was approximately twenty.

A. That's what I remembered, yes.

MR. HOFFMAN: Okay, thank you.

THE COURT: Okay, Dr. Garvey. Thank you very much.

THE WITNESS: You're welcome very much.

MR. HOFFMAN: Your Honor, may we approach before the jury leaves?

THE COURT: Certainly.

MR. HOFFMAN: Over lunch Mr. O'Rourke and I talked and we've decided we're not going to call Nurse Patch.

THE COURT: Okay.

MR. HOFFMAN: And Dr. Greenblatt has told us he's going to get in his car at 6 a.m. and be here between 10 and 10:30. I'd like a little time with him. Would it be possible to start at, say, noon? I don't ex-

pect it will be long with him. Richard, I don't expect you're going to cross him.

THE COURT: Only one witness

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MARCH 12, 2004

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[Testimony of Dr. David J. Greenblatt]

[17] looked at, correct?

A. Yes.

Q. And I'm going to hand you a copy of the labeling that's already been marked. Take a look at it again. Do you have an opinion whether the labeling information provided concerning the risk of arterial injection of this product or inadvertent intra-arterial injection was accurate?

A. Yes, I do.

Q. Okay. Could you explain why?

A. I think the warnings are severe, given in multiple places in bold letters with the—the risks and the very bad consequences clearly outlined and warned against.

Q. Okay. Does the labeling provide enough instruction to physicians or physician's assistants for the safe use of the product?

A. Yes.

Q. Why do you believe that?

A. Well, it is known, for example, for this specific circumstance, that you have to have an intravenous access that is functioning properly for this drug to be given safely by the intravenous route of administration.

[18] It's very clear, and it's also clear what happened if that fails.

Q. Okay. What is "functioning properly" or "functioning satisfactorily," the verbiage in the label; what does that mean?

A. That means that the IV access is secure, that it's clearly in the vein, and that the fluid that is going in is clearly flowing into a vein and not into an artery and not outside the vein.

Q. And so we're clear, do you think that a butterfly infusion set is—can be a set that can be used with this medication?

A. Yes, it certainly can be.

Q. Okay, but, well, do precautions need to be taken to use that?

A. Absolutely.

Q. What kinds of precautions?

A. One, the administrator has to be very certain that the butterfly needle is—

MR. RUBIN: Objection. Can we approach?

THE COURT: Sure.

(At the bench):

MR. RUBIN: Again, he's not an

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[26] knows how to read what secondary literature is out there, knows what the risks are.

THE COURT: I'll overrule the objection.

(In open court):

BY MR. HOFFMAN:

Q. Can I trouble you to read back the question. I've really forgotten it.

THE COURT REPORTER: "Let me ask you about risk/benefit now, specifically with respect to Phenergan. Do you think the IV use of Phenergan should be used"—

MR. HOFFMAN: Banned.

Q. Do you think the intravenous use of Phenergan should be banned, Doctor?

A. I don't think it should be banned.

Q. Why not?

A. This medication is given intravenously extensively throughout the United States and throughout the world. There are clinical situations in which to produce the needed relief of the patient that IV may be the preferable or the only way it may be administered. There are obvious risks to IV administration and they are extensively and [27] adequately warned against and, if the treating physician decides that the need to produce relief on that patient is urgent, then it's reasonable to give the drug IV to produce that relief if it's done properly.

Q. Why not give it as an intramuscular injection?

A. There are instances in which intramuscular injection is unreliable. Oftentimes an intramuscular injection, particularly in people who are overweight, may not actually get into a muscle but be injected into fat and be poorly absorbed. There may be cases in which somebody is seriously ill and has poor blood flow to a muscle, to the various muscle groups, because they may be dehydrated or they may have cardiac disease or something else is wrong with them, and even an injection that gets into a muscle may not be absorbed, so

there are circumstances in which an intramuscular injection is unreliable.

Q. Have you done studies about intramuscular injections?

A. Yes, we have.

Q. What about other therapies, aren't there

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[32] in order to provide that kind of opinion?

A. I believe so.

Q. Let me ask you one last question?

A. Yes.

Q. Okay. How can it be that the benefits of getting a little quicker treatment of nausea or a little better treatment of nausea justify running the risk of the kind of terrible event that took place here?

A. Well, it's a judgment that is made by a treating physician who's treating a given patient and, if there is serious distress due to nausea and vomiting, if it won't stop, if the patient is miserable, if the patient is losing fluid and becoming dehydrated and very ill, then the physician in that urgent situation looks at what's available and, with knowing the risks of IV promethazine, would nonetheless make a judgment that the benefit to the patient is worthy of accepting that risk, and it's a clinical judgment when we're trying to, you know, when people are trying to take care of sick patients.

MR. HOFFMAN: I have no further questions. Thank you very much, Dr.

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[35] done, it's not just me. There's a large research group, a number of people that I work with, so we do it.

Q. I understand that, but I think what would help us is your particular personal interest is in these areas, and then you work on a team to accomplish the results, right?

A. In part, yes.

Q. You're the chair of this Department?

A. Correct.

Q. And it has an endowment, it's an endowed chair?

A. In part, yes.

Q. In connection with your work as a clinical pharmacologist, I think you told Mr. Hoffman that some portion of the work or the studies that you do are funded by the drug companies that have an interest in the drugs that's being studied?

A. In some cases a small fraction overall has been supported by private sources.

Q. It is true that in the cases where you're working on the drugs that it's sometimes supported in part by the drug companies that have an interest in the medication that [36] you're testing?

A. Say that again. I didn't—

Q. I'm just asking whether you, in fact, get money from drug companies to assist in your research? And I know you said it's a small part, but that is true, right?

A. I don't get it personally, the University gets it, but there is support from pharmaceutical companies in some cases to assist in doing research.

Q. Okay. And, in fact, when you do research and complete your results, often you will publish those results in peer-review journal—medical journals?

A. Essentially all the time, yes.

Q. So, when the work is done, you publish the results for other professionals to share and learn from?

A. Correct.

Q. Actually, I did a little research about some of the studies that you've done. Lorazepam is a product made by whom?

A. By Wyeth.

Q. And in—I think first one I found was in 1977, you did a published a study with the [37] lead author called "Clinical pharmacokinetics of lorazepam"; do you remember that one?

A. Not specifically. Yes, that's correct.

Q. And Wyeth was acknowledged as one—one of the contributing fenders of that study?

A. Yes.

Q. I found another one, 1978, where you were the lead author of a study called "Analysis of lorazepam and its—some chemical component?

A. Yes, glucuronide metabolite.

Q. Right?

A. Right.

Q. And Wyeth helped or assisted in the funding of that study?

A. That's correct.

Q. I think I found another one in 1979, "Pharmacokinetics and bioavailability of oral lorazepam in humans or all different kinds of lorazepam in humans," '79, again you were the lead author in that one?

A. Yes, that's correct.

Q. That was a—Wyeth assisted in these?

A. All of these studies were principally funded by the National Institute of Health, but there was additional support beyond.

[38] Q. And this was a Wyeth product?

A. That's correct.

Q. There was another one I found more recently in 1998, I'm going to get this one wrong, "Comparative kinetics and dynamics on of zaleplon, zolpidem, and a placebo"?

A. Yes.

Q. Zolpidem is a Wyeth product, right?

A. Yes. We mentioned that in direct testimony.

Q. Okay, so that was 1998?

A. Yes.

Q. And that was assisted by a grant and aid from Wyeth-Ayerst Research in Radley, Pennsylvania?

A. That's right.

Q. I don't know if you mentioned this one, you might have, here's another one, "Kinetics and dynamics of lorazepam," you were the lead author in the Year 2000. Was that a similar study of Xanax or lorazepam?

A. This is Ativan, lorazepam, this was also mentioned in direct testimony.

Q. Performed in 2000?

A. Well, the study was actually done in the early—as discussed, it was done in the [39] earlier '90s but did not get published until 2000.

Q. And that got some grant funding from Wyeth, too?

A. That's correct.

Q. You got the appointment to the chair of this department in I think it's 1997?

A. '94.

Q. Okay. I saw a kind of a press release from Tufts which said "Tufts Professor Appointed to Pharmacology Chair," and appears to be referring to you. And this is called the Dr. Lasagna chair?

A. Yes.

Q. He's a well-reknown former clinical pharmacologist?

A. Yes.

Q. And this chair, professorship chair, was established with a million and a quarter dollars in private donations, including more than $650,000 from pharmaceutical companies?

A. Um, I'm not familiar with the source, but there is an endowed share, yes.

Q. And the pharmaceutical companies contribute generously and appropriately to the chair, to [40] the funding of this chair?

A. I believe that's the case, but I honestly don't know the details.

Q. In connection with your work, you also, as other doctors do, participate in seminars and meetings where you exchange information with other professionals on relevant topics?

A. Yes.

Q. Okay, and you are a member or are you a member of the American College of Clinical Pharmacology?

A. I am.

Q. I have a copy of a program from September 2002, it looks like it was a kind of some educational work that was done in connection with the annual business meeting. Do you happen to remember that in 2002?

A. If you let me look at it, maybe I'll remember.

Q. Sure. Take a look at page 13?

A. Yes.

Q. In that particular meeting you—it was actually a seminar. It appears to be on the relationship between some form of legal liability and your profession, right?

[41] A. Well, my particular role was to talk about the role of institutional review boards and clinical research in general.

Q. Fair enough. But this teaching forum was supported, as is usually the case or often the case, by educational grants by various drug companies, including Wyeth?

A. Could be. Yup.

Q. You work in a hospital setting?

A. Medical school setting.

Q. Do you work at the New England Medical Center downtown or do you work at Tufts?

A. Tufts University School of Medicine, which is across from New England Medical Center.

Q. That's in downtown Boston?

A. Yes.

Q. So it's a separate building but part of that New England Medical School's complex?

A. Two separate institutions. The medical school is part of Tufts University, which is actually the main University is in Medford, but Tufts New England Medical Center is a different corporate entity, and that's a hospital, and it's the main teaching hospital for Tufts University but it's—they're not [42] otherwise connected.

Q. Okay, so they've got the same first name but they're actually legally different?

A. Yes.

Q. You work at the Medical School?

A. My primary appointment is at the Medical School.

Q. But your clinical studies are done in the Hospital?

A. No, most are done in a clinical unit right in our own Medical School Department, but some clinical studies are done in the Hospital, in the general Clinical Research Center.

Q. So primarily you're working in a clinic, a clinic, if you will, which is part of your department at the Medical School?

A. Yes.

Q. Okay. And you don't treat migraine headaches?

A. No, I don't.

Q. And you don't prescribe antinausea drugs?

A. Correct.

Q. And from 1974 to 1990 I think you told me that less than five percent or less of your time was actually in the clinical practice of [43] medicine?

A. Correct.

Q. Essentially since you graduated from—completed your residency and perhaps some fellowship training, you have been doing clinical research as your primary work?

A. Basic and clinical research that's correct.

Q. And those five percent of the people that you did carry or see through 1990 were actually people who had been in a high blood pressure study; that was, while you were a resident, you kind of followed them along, or did I get that wrong?

A. No, they weren't in a study. As part of my fellowship training, we did outpatient clinic duty and, because my mentor treated hypertension, most of the patients that I acquired had primary disorder of high blood pressure, and I continued to follow them after training up until about 1990.

Q. Okay, and that was about five percent of your time?

A. No more than five percent.

Q. Since 1990, you have not had any clinical practice at all?

* * *

[45] or are healthy before they participate?

A. Most are, but not entirely. We do a lot of research in AIDS and HIV medications and those—most of those people are infected with HIV. Some are also normal volunteers, and there are studies like that that involve patients, but we don't treat the patients, themselves, they're participants in the studies.

Q. Since—I think you told Mr. Hoffman, since your training, you have no experience with Phenergan?

A. That's correct.

Q. Or any other antinausea drug to treat migraines?

A. I have not treated migraine.

Q. And you didn't undertake any independent research on the safety of Phenergan for IV use; you're relying on the warnings here, primarily?

A. What do you mean by "independent research"? I didn't do any studies.

Q. All right. You didn't talk to anybody at the FDA?

A. No.

[46] Q. Did you talk to anybody at Wyeth who has any role with this drug?

A. No.

Q. And I asked you what your general knowledge of Phenergan was, what your knowledge of Phenergan was, and it's true that you only had a general knowledge of its properties as a psychotropic drug?

A. Yes, I know that it's a thiephyazine, it has antihistaminic properties, which probably was why it's an antinausea drug. It does interact with the dopamine receptor which is an additional method by which it has antihistaminics properties, but it's not strong enough to be used, for example, with schizophrenia, for example, or psychosis.

Q. So you didn't talk to anybody at Wyeth about the drug. Did you, in fact, when I talked to you in November of 2002, you didn't even know whether it was used at your hospital?

A. Correct. I still don't.

Q. You don't know, then, clearly, if it is used at the hospital next door, how it's administered in the Emergency Department?

A. I don't know whether it's used at all or

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[49] A. Well, you still have to have access to the vein, so the needle insertion into the vein is what determines where it is. The infusion set is simply the—the means of administering the fluid into the vein by means of whatever needle you use.

Q. In fact, when you and I have talked, you—you thought that the warnings already required a free-flowing IV system, right?

A. I believe the warnings require a properly-functioning IV, which can—which does include free-flowing. It doesn't necessarily mean a hanging IV. A butterfly tube connected to a syringe could be functioning properly, as well.

Q. Could you open to page 46?

A. Um-hum.

Q. And actually line 23. I'm going over to line 2 on page 47.

A. Yes.

Q. And there's a question I asked you?

A. Um-hum.

Q. "So it's your opinion that the instructions do say it's preferable to put it through a free-flowing IV?" And your answer was:

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[77] because they knew it was unsafe. They should have pulled their drug the way Pfizer pulled theirs from intravenous use. At a minimum, they should have required that you use a free-flowing IV. You've heard the discussion about how that free-flowing IV, that tube, and you guys can play with this in the jury room, or not, when you set that up and you let that saline run into the vein for a few minutes, you're going to know you're in the vein, it's got that soft catheter, you saw that, that bends. It's not going to migrate out of the vein. You use that, you know that you're not in an artery, because the back pressure of the artery is ten times the venous pressure and it stops the flow. Everybody said—except Dr. Garvey who I'll talk about in a minute, everybody said that, if it gets under the skin, it forms a little bubble, stops the flow, so you know, if you use that system, it's not a hundred-percent safe but it sure is a lot safer, and Wyeth knew it, too. And Dr. Greenblatt knew it, because he thought it was already in there.

I want to talk about the FDA. The [78] FDA this, the FDA that. Thank God we don't rely on the FDA to rely on this drug and make the safe decision. You will make the decision.

Dr. Garvey gets 750 an hour. I figured out, after he left Washington, worked 'til nine o'clock, started next morning, fifteen hours, he made probably between ten to fifteen thousand bucks to come up, 750 an hour.

Dr. Greenblatt is a prominent scientist. I'll talk about his opinion in a second. He gets two hundred dollars an hour. What are they paying Dr. Green—Dr. Garvey for? I'll tell you what they're paying him for. He came in here and said to you, I couldn't believe it, he

said, Oh, once Wyeth had that warning there, this one here, they couldn't change it without FDA approval. He said that you can't change it without FDA approval. I said, Really? You mean they can't change it to a free-flowing IV? He said, No, can't do it, gotta get prior approval, and he cited some old federal regulation.

* * *

[81] updated warning on inadvertent intra-arterial injection and perivascular extravasation, that's the leakage, becomes available to doctors and nurses since misinjection may cause severe tissue injury, and we believe the use of the updated warning is of critical importance for the safe use of Phenergan injection.

They never made the change. They could have, they didn't, and for some reason in 1998, why, the FDA says use the old warning. The FDA doesn't make the decision, you do. Wyeth was negligent, they were remiss, and their behavior, conduct, is unexplainable and inexcusable. They're certainly not justified.

Where's the witness? Look at the chair. Where's the witness from Wyeth that says, Well, let me explain to you, ladies and gentlemen, why we didn't change it, why we thought—you know, why we didn't initiate this. Let someone come in here besides Dr. Garvey and tell you, We didn't change this instruction or we thought the existing instruction was better, nobody. The FDA

* * *

[83] don't say that with the 25. If this can do the damage that it did, we can assume and it seems to be the evidence that the 50 is too dangerous because, if it gets into your artery or leaks around or invades your artery, you're in trouble. But the evidence is the 25 will do exactly the same thing.

Dr. Green talked about the adverse events reporting the 25 dosage did exactly the same thing, so what are they doing? Where's the witness that will explain to you why they say don't use that 50-milligram dose intravenously, but it's okay -- I get a little choked up—it's okay to use the 25. Nobody comes up here. The reality is, neither one of them is safe for intravenous use with a butterfly, neither one of them. For thirty years they have known that and continued to market. You know, one thing that was interesting was they send their sales people up here to market their drugs, Marty Fitzgerald, to go by The Health Center a couple times a month, and they market their drugs, they sell the drugs. They're called detail men in the trade, and they hand out

* * *

[Jury Instructions]

[145] THE COURT: All right, it's now my job to give you the Court's instructions regarding the law to apply in your deliberations. You'll get—you don't have to memorize, it you'll get a copy of the charge, each one of you, downstairs, so don't feel this is the only time you'll get to look at it, okay.

Ladies and gentlemen of the jury, now that you've heard all of the evidence and the arguments of counsel, it becomes my duty to give you the instructions of the Court concerning the law which governs this case. It is your duty as jurors to follow the law as I state it to you and to apply that law to the facts as you find them from the evidence presented in court. You're not to single out one instruction alone as stating the law. You should consider the instructions as a whole. Nor are you to be concerned with the wisdom of any rule of law stated by me. Regardless of any opinion you may have as to what the law is or ought to be, it would be a violation of your

sworn duty to base a verdict upon any view of the law other than [146] that given in the instructions of the Court. Similarly, it would be a violation of your sworn duty as judges of the facts to base a verdict upon anything other than the evidence presented during the trial.

Your job is to decide the facts based on what you heard and saw during the trial. This includes the testimony of the witnesses and the exhibits admitted by me. You will be given the exhibits in the jury room. In deciding the facts, you must not be swayed by sympathy or prejudice towards either side.

My job is to give you the law. After you decide the facts, you need to apply the law that I give you, even if you do not agree with it. Remember that statements, objections, or arguments made by the lawyers are not evidence in the case. The lawyers' job is to point out those things that are most significant or most helpful to their side of the case, which you otherwise might not have noticed. You should also not assume from any statements that I may have made that I have any opinion about how you should [147] decide this case.

In considering the evidence, you are not limited to the bare statements of the witnesses. You may draw reasonable conclusions from the testimony and exhibits based on common sense and experience. However, you may not guess about what testimony or exhibits that were not admitted into evidence might have shown.

Credibility of witnesses. You must consider all of the evidence. This does not mean that you must believe all of the evidence. You are the sole judges of the reliability of each witness and the weight that each witness's testimony should be given. In evaluating the testimony of witnesses, you should consider whether they have any interest in the outcome of the case, their

demeanor while testifying, their candor, any bias they might have, and the extent to which other believable evidence in the case fits with their testimony. You should also consider their ability or opportunity to see or hear the facts about which they have testified, and whether they [148] remember these facts accurately. You may believe as much or as little of each witness's testimony as you think appropriate. Keep in mind that people sometimes forget things or make mistakes in their testimony. You must decide whether an error is innocent or minor or something more which affects the rest of their testimony.

Expert Witnesses. Some witnesses testify for the purpose of giving an opinion on the basis of special knowledge. In this case both sides called expert witnesses. These include doctors and persons with other scientific expertise. First, you should evaluate an expert witness in the same way you would any other. Then you should evaluate whether the opinion is well grounded in approved facts and supported by the witness's learning and experience.

Burden of proof. Ms. Levine must prove each element of her claims by a preponderance of the evidence. A preponderance of the evidence means the more convincing evidence. It does not mean the most witnesses. It is a matter of quality, [149] not quantity. If the evidence tends to be equally balanced, the party who has the burden of proof cannot proceed on his or her claim. Think of the test as the 51 percent rule, in light of the evidence and the law, do you believe that the claim is more likely true than not.

Now, the Claims. Plaintiff, Diana Levine, makes two claims against Wyeth. These are that Wyeth acted negligently in failing to provide adequate instructions

to the physicians or other medical professionals about the use of the drug Phenergan and that Wyeth is strictly liable for failing to warn of the risks of the drug Phenergan. Wyeth denies both these claims and states that the warnings and instructions were adequate and they were not the cause of Ms. Levine's injury. You should consider each of these claims separately.

FDA Regulation. Before I instruct you about the elements of the Plaintiffs claim, I will say a word about the FDA. You may consider evidence of compliance by Wyeth with FDA requirements in obtaining approval **[150]** for the Phenergan warning. Compliance with the FDA requirements, by itself, does not establish that the warning was adequate for purposes of this case. You must decide whether the instructions and warning were adequate based upon all of the evidence presented in this trial including evidence about the FDA process. The FDA regulations, 21 CFR section 314.70, permit a drug manufacturer to change a product label to add or strengthen a warning about its product without prior FDA approval so long as it later submits the revised warning for review and approval.

Now, the Claims: Negligence. A claim of negligence has three essential elements: A duty of care, breach or violation of that duty, damage or injury caused by the breach of duty. I'll discuss each one of these with you in the context of this case.

Duty of care: The manufacturer of a product such as Wyeth has a duty to take reasonable steps to notify users of the product, in this case the medical community, **[151]** of the risks and dangers of the product and to provide adequate instructions about how to use the product safely. This standard of conduct of reasonable care does not require that useful drugs with dangerous

potential be removed from the market; instead, the law requires that Wyeth exercise reasonable care to warn or protect against the risks. The standard is what would a reasonable manufacturer have done under similar circumstances to provide warning and instruction about the risks of the product.

Warnings for prescription drugs are intended for the physician and staff whose duty it is to balance the risks against the benefits of various drugs and treatment and to supervise their effects. You may consider the facts you have heard about in the course of this trial, including the seriousness of the risks to patients, the likelihood or incidence of injury, and the content of warning and advice provided by Wyeth.

Duty to warn: First you have to determine the nature and extent of Wyeth's duty to warn and advise about a—duty to [152] warn and advise about the risks of injury the patients—to patients presented by Phenergan. You must decide the extent to which Wyeth should have warned and advised of the risks and injuries which could result from an injection of Phenergan of the type conducted in this case. The manufacturer's duty is to warn of all potential dangers in its prescription drugs that it knew or in the exercise of reasonable care should have known to exist. It's for you to decide the nature and scope of the warning required.

Violation of duty: After you've determined the nature of the warning required, you must consider whether the information presented by Wyeth to physicians at the time Ms. Levine received the drug complied with this duty or fell short of compliance. In other words, you must decide what a reasonable drug manufacturer should do to inform physicians about the risks and potential harm presented by Phenergan when

administered by injection, and then you must decide whether Wyeth's action met the standard or not. The warning must reasonably [153] advise of the risks and provide adequate instructions to the physician or other medical professional for its safe use.

Causation. If you determine that Wyeth breached its duty to warn, you must determine whether any breach of the duty to warn caused Ms. Levine's injuries. You should consider whether an adequate warning or instruction would have been read and followed, and whether reading and following an adequate warning would have prevented Ms. Levine's injuries. Bear in mind on the issue of causation that an event may have several causes. Some of these causes are very direct and obvious, others are more remote. Your job in determining legal cause is to ask yourselves this question: Did the Defendant's negligence lead to the Plaintiff's injury in an understandable chain of cause and effect. The law does not require that the negligent act be the sole cause of the injury. Several factors may combine to cause an injury. The Plaintiff is required to show that an act of negligence by the Defendant was a substantial factor in [154] causing her injury.

Intervening event. Wyeth claims that the action of Ms. Fisch in continuing to administer Phenergan to Ms. Levine after Ms. Levine complained of pain was an intervening event which breaks any causal connection between the product warnings and instructions and Ms. Levine's injury. On this issue, Wyeth has the burden of proof by a preponderance of the evidence, which means more likely than not. In order for an event to break the chain of causation between an initial act of negligence and the injury, the intervening event must be unforeseeable by Wyeth. The intervening event must also be, itself, a cause of the injury. The chain of causation is

broken if you find that Wyeth could not anticipate that a physician's assistant in Ms. Fisch's position would complete the injection after the complaint of pain and that stopping the injection when Ms. Levine complained of pain would have prevented her injury. You must decide if Wyeth has met its burden of proof on intervening cause. If you find that it has, [155] then you should find that Wyeth's conduct, even if negligent, was not a cause of injury for purposes of this lawsuit. If you decide that Wyeth was negligent and that this negligence was a cause of Ms. Levine's injury, you should find for Ms. Levine on this issue. If you find that Wyeth was not negligent and that any cause was not a cause of or that an intervening event broke the chain of causation, you should find for Wyeth on this issue. In either event, you should now consider the claim of strict liability.

Now I'm going to get a glass of water.

Strict Liability. Failure to Warn: A manufacturer of a product such as Phenergan is responsible for harm to a person caused by a defective product that reaches a user without undergoing substantial change. In this case there is no dispute that Ms. Levine was injected with the drug Phenergan which was manufactured by Wyeth and that the product was not changed between the date it was manufactured and the time of injection. The parties disagree over whether the drug [156] was defective as a result of inadequate warning.

In this case the term "defective" means unreasonably dangerous. A prescription drug is unreasonably dangerous due to inadequate warnings or instructions if reasonable instructions or warnings regarding foreseeable risks of harm are not provided to the physician and other medical professionals who are in a position to reduce the risks of harm. Just as in the neg-

ligence claim, the disputed issue is whether the warning and instructions provided by Wyeth were adequate concerning the risks of injection of Phenergan. The warning must reasonably advise of the risks and provide adequate instructions to the medical professionals for its safe use. This is the critical factual issue which you must decide on the basis of the evidence of the risks and benefits of intravenous administration and the potential for injury to patients.

Causation. Finally, if you decide that the warning or instruction was inadequate, you must decide whether this [157] inadequacy was a cause of the injury. You should consider whether an adequate warning or instruction would have been read and followed and whether reading and following an adequate warning or instruction would have prevented Ms. Levine's injuries. As in the case of the negligence claim, you should bear in mind that the law does not require that an inadequate warning or instruction be the sole cause of the injury. Several factors may combine to cause the injury. The Plaintiff is required to show that an inadequate warning or instruction was a substantial factor in causing her injury.

The defense of intervening event also applies to the strict liability claim. Wyeth has the burden of proof on this issue by a preponderance of the evidence. If you find that Wyeth has shown that the action of Ms. Fisch, in continuing to administer Phenergan to Ms. Levine after her complaint of pain was not foreseeable by Wyeth, and that stopping the injection when Ms. Levine complained of pain would have prevented her injury, then you should find for Wyeth on the [158] issue of causation. You should reach a decision on your verdict form on both the issues of negligence and strict liability.

Damages. If you decide in favor of the Defendant on both counts of negligence and strict liability, you should enter a verdict for the Defendant on the verdict form and cease your deliberations. You will not consider these instructions about damages. But, if you decide in favor of Ms. Levine on either the claim of negligence or the claim of strict liability or on both claims, you shall award Ms. Levine an amount of money that you believe will put her as nearly as possible in the position she would have occupied if the injury to her right arm had not happened. Here are some further instructions to help you do that. Ms. Levine has the burden of proof by an preponderance of the evidence on each element of her claim for damages.

Personal injury damages. Ms. Levine is entitled to compensation for any bodily injury and any pain and suffering, disability, disfigurement, mental anguish, [159] and loss of enjoyment of life experienced in the past or probably to be experienced by her in the future. You should award monetary compensation for these damages for any harm you find caused by the injury to her right arm and related conditions. There is no particular formula to calculate this compensation. You should make sure that any amount awarded to Ms. Levine is fair, just, and reasonable, in light of the evidence you have heard.

Medical expenses, personal care, and equipment: Ms. Levine is entitled to compensation for the cost of medical treatment, personal care treatment, and modifications of her home, reasonably necessary in the past or that will probably be necessary in the future because of the injury to her arm.

Lost earnings and earning capacity. Ms. Levine is entitled to compensation for any lost earnings in the past and any probable loss of ability to earning in the future

because of her injury to her right arm. When considering Ms. Levine's future **[160]** earnings, you should consider her expected working lifetime. Reasonable, not speculative damages must be supported by the evidence. You must not award damages based upon speculation.

Income taxes. If you find for Ms. Levine, you must not consider any effect of federal or state income tax in deciding the award.

Interest. The Court will resolve the issue of interest on any damages following your verdict. You should not add any additional amount of your award for interest.

Recovery from any other source. In this case you heard evidence that there was a claim against the physician and The Health Center. This evidence was admitted for the limited issue of credibility. I discussed this issue with you at the time. I instruct you now that you should not speculate or consider the effect of any other recovery or payment from another source in considering the issue of damages. If you award damages, the amount should be for the full amount of **[161]** Ms. Levine's loss as you determine it.

Foreperson. The Court appoints Barbara Butler as your foreperson. She will be responsible for guiding your deliberations and making sure that everyone is able to participate fully. Your verdict must be unanimous. A verdict form will be provided for your use, and you will also receive the exhibits in a couple of minutes.

And that concludes my instructions.

Counsel want to approach?

(At the bench):

MS. DeWOLFE: Your strict liability portion of the charge, you changed in one of the instructions. I asked

that you did that in negligence. I'm assuming the jury will infer there was some distinction when you say "warnings" and "warnings and instructions." That's a bit of a hassle, but I think it's important. No. 2, we would object to your decision not to give the so-called "Read and Heed Presumption," Bridport V. Sterling case, and I continue to object to the intervening negligence charge that's been given here and, instead, would request the instruction I [162] drafted on causation. I think that does it. Thank you very much.

MR. KEYES: The objections, the first is on the failure to charge comparative fault between The Health Center. We filed a request to charge and a trial memo on that issue and asked for the jury to determine a comparative negligence between the two. Both have been sued. On intervening cause, we feel the Patent v. Sawyer case is an exception to the rule, that there's no intervening cause when we have a duty to anticipate the negligence and that is exception when the intervening actor becomes aware of the risk and knowingly proceeds. We submitted a supplemental charge on intervening cause this morning and object to the Court's failure to include that, and, third, is an objection to the Court's failure to have a charge on reduction to present value for future losses, both generally and particular to the closing argument which was asking for an hourly computation of future losses.

THE COURT: Okay. Good enough. [163] Your objections are noted. Thank you.

MS. DeWOLFE: Thank you, Judge.

THE COURT: Okay.

(In open court):

THE COURT: Okay, you can retire to your jury room and start your deliberations. Before you go, let me just say this, that your work now is the most important thing that this court has going, so take all the time you need, and we'll stay late for you, as long as, Ms. Butler, as everybody is working in a productive, helpful way, we'll stay 'til you tell us okay, and the State will buy you some dinner.

(The jurors left the courtroom at 3:43 p.m)

(In open court at 5:06 p.m.):

THE COURT: All right, we're back on the record; and, Mr. O'Rourke, did you want to offer an exhibit?

MR. O'ROURKE: Yes, Court's Exhibit JJ, which is the Covenant, your Honor. We'd like to offer that.

THE COURT: Is it confidential in some way?

* * *

[Jury Verdict]

[166] amount up to that number, which we believe to be around $220,000 pre-judgment interest, statutory rate will be computed upon that amount. We're specifically waiving any pre-judgment interest on past lost wages because of a strategic decision about how we wanted the verdict form designed.

MR. O'ROURKE: Pre-judgment will be worked out between Kerry and myself.

THE COURT: On the basis of the dates the charges were incurred?

MS. DeWOLFE: Correct.

(Court was in recess from 5:11 p.m. until 7:52 p.m.)

THE COURT OFFICER: Members of the jury, has the jury reached a verdict?

THE FOREPERSON: Yes, we have.

(The court officer approached the bench.)

THE COURT OFFICER: In the case entitled Diana Levine vs. American Home Products, Inc., now Wyeth, this is the verdict of the jury.

Question 1: Do you find that Wyeth was negligent in this case?

[167] Answer: Yes.

Question 2: Was the negligence of Wyeth a cause of Diana Levine's injuries?

Answer: Yes.

Question 3: Did an intervening cause break the causal connection between Wyeth's negligence and Diana Levine's injuries?

Answer: No.

Question 4: Was the product Phenergan defective when administered to Diana Levine as a result of inadequate warnings and instructions?

Answer: Yes.

Question 5: Were the inadequate warnings or instructions a cause of Ms. Levine's injuries?

Answer: Yes.

Question 6: Did an intervening cause break the causal connection between a defect in the product Phenergan and Ms. Levine's injuries?

Answer: No.

Question 7: Please state the amounts of damages you award for the following elements of Ms. Levine's claim:

Economic losses and costs, medical [168] care, medical expenses, personal care, and equipment costs, lost earnings, and earnings capacity: 2.4 million dollars.

Non-economic losses, personal injury damages: Five million dollars.

Do you wish the jury polled?

Do you wish the jury polled?

MR. O'ROURKE: No, your Honor.

THE COURT: And, Ms. Butler, is this the verdict of the jury?

THE FOREPERSON: Yes, sir.

THE COURT: Thank you all for your service. I think you've all—

Is there anything to take up with the jury from either of you?

MR. O'ROURKE: I don't think there is, your Honor.

MR. RUBIN: No. In fact, thank you, your Honor.

THE COURT: I think you can all go. I thank you very much for your service in this case.

(The jurors left the courtroom.)

THE COURT: Okay, have a seat, please.

* * *

STATE OF VERMONT
COUNTY OF WASHINGTON, SS.

DIANA LEVINE

v.

Washington Superior Court
Docket No.: 670-12-01

AMERICAN HOME PRODUCTS, INC.
(Now Wyeth).

JURY INSTRUCTIONS

Ladies and gentlemen of the jury:

Now that you have heard all of the evidence, and the arguments of counsel, it becomes my duty to give you the instructions of the court concerning the law which governs this case.

* * *

CLAIMS

Plaintiff Diana Levine makes two claims against Wyeth: these are that Wyeth acted *negligently* in providing information to physicians and medical personnel about the risks fo the drug Phenergan and that Wyeth is *strictly liable* for failing to warn of the risks of the drug Phenergan. Wyeth denies both of these claims and states that the warnings and instructions were adequate and that they were not the cause of Ms. Levine's injury. You should consider each of these claims separately.

FDA Regulation

Before I instruct you about the elements of the plaintiff's claim, I will say a word about the FDA.

You may consider evidence of compliance by Wyeth with FDA requirements in obtaining approval for the Phenergan warning. Compliance with the FDA re-

quirements by itself does not establish that the warnings was adequate for purposes of this case. You must decide whether the instructions and warnings were adequate based upon all of the evidence presented in this trial including evidence about the FDA process.

The FDA regulations, 21 C.F.R. S 314.70, permit a drug manufacturer to change a product label to add or strengthen a warning about its product without prior FDA approval so long as it later submits the revised warning for review and approval.

Negligence

A claim of negligence has three essential elements: a duty of care; breach or violation of that duty; damage or injury caused by the breach of duty. I will discuss each one of these with you in the context of this case.

Duty of Care

The manufacturer of a product such as Wyeth has a duty to take reasonable steps to notify users of the product—in this case the medical community—of the risks and dangers of the product and to provide adequate instructions about how to use the product safely. This standard of conduct of reasonable care does not require that useful drugs with dangerous potential be removed from the market. Instead, the law requires that Wyeth exercise reasonable care to warn or protect against the risks.

The standard is what would a reasonable manufacturer have done under similar circumstances to provide warning and instruction about the risks of the product. Warnings for prescription drugs are intended for the physician and his staff whose duty it is to balance the risks against the benefits of various drugs and treatments and to prescribe them and supervise their effects. You may consider the factors you have heard

about in the course of this trial including the seriousness of the risk to patients, the likelihood or incidence of injury, and the content of the warning and advice provided by Wyeth.

Duty to Warn

First, you have to determine the nature and extent of Wyeth's duty to warn and advise about the risks of injury to patients presented by Phenergan. You must decide the extent to which Wyeth should have warned and advised of the risk and injuries which could result from an injection of Phenergan of the type conducted in this case. The manufacturer's duty is to warn of all potential dangers in its prescription drugs that it knew, or in the exercise of reasonable care, should have known to exist. It is for you to decide the nature and scope of the warning required.

Violation of Duty

After you have determined the nature of the warning required, you must consider whether the information presented by Wyeth to physicians at the time Ms. Levine received the drug complied with this duty or fell short of compliance. In other words, you must decide what a reasonable drug manufacturer should do to inform physicians about the risks and potential harm presented by Phenergan when administered by injection and then you must decide whether Wyeth's actions met this standard or not. The warning must reasonably advise of the risks and provide adequate instructions to the physician or other medical professional for its safe use.

Causation

If you determine that Wyeth breached its duty to warn, you must determine whether any breach of the duty to warn caused Ms. Levine's injuries. You should con-

sider whether an adequate warning or instruction would have been read and followed and whether reading and following an adequate warning would have prevented Ms. Levine's injuries.

Bear in mind on the issue of causation that an event may have several causes. Some of these causes are very direct and obvious. Others are more remote. Your job in determining "legal" cause is to ask yourselves this question: did the defendant's negligence lead to the plaintiff's injury in an understandable chain of cause and effect?

The law does not require that the negligent act be the sole cause of the injury. Several factors may combine to cause an injury. The plaintiff is required to show that an act of negligence by the defendant was a substantial factor in causing her injury.

Intervening Event

Wyeth claims that the action of Ms. Fisch in continuing to administer Phrenegan to Ms. Levine after Ms. Levine complained of pain was an "intervening event" which breaks any causal connection between the product warnings and instructions and Ms. Levine's injury. On this issue, Wyeth has the burden of proof by a preponderance of the evidence which means more likely than not.

In order for an event to break the chain of causation between an initial act of negligence and the injury, the intervening event must be unforeseeable by Wyeth. The intervening event must also be itself a cause of the injury. The chain of causation is broken if you find that Wyeth could not anticipate that a physician's assistant in Ms. Fisch's position would complete the injection after a complaint of pain and that stopping the injection when Ms. Levine complained of pain would have prevented her injury.

You must decide if Wyeth has met its burden of proof on the issue of intervening cause. If you find that it has, then you should find that Wyeth's conduct, even if negligent, was not a cause of the injury for purposes of this lawsuit.

If you decide that Wyeth was negligent and that this negligence was a cause of Ms. Levine's injury, you should find for Ms. Levine on this issue. If you decided that Wyeth was not negligent, that any negligence was not a cause of Ms. Levine's injury or that an intervening event broke the chain of causation, you should find for Wyeth on this issue. In either event, you should now consider the claim of strict liability.

Strict Liability—Failure to Warn

A manufacturer of a product such as Phenergan is responsible for harm to a person caused by a defective product that reaches a user without undergoing substantial change. In this case, there is no dispute that Ms. Levine was injected with the drug Phenergan which was manufactured by Wyeth and that the product was not changed between the date it was manufactured and the time of injection. The parties disagree over whether the drug was defective as a result of inadequate warning.

In this case, the term "defective" means unreasonably dangerous. A prescription drug is unreasonably dangerous due to inadequate warnings or instructions if reasonable instructions or warnings regarding forseeable risks of harm are not provided to the physician and other medical professionals who are in a position to reduce the risks of harm.

Just as in the negligence claim, the disputed issue is whether the warning and instructions provided by Wyeth were adequate concerning the risks of injection

of Phrenagen. The warning must reasonably advise of the risks and provide adequate instructions to the medical professionals for its safe use. This is the critical factual issue which you must decide on the basis of the evidence of the risks and benefits of intravenous administration and the potential for injury to patients.

Causation

Finally, if you decide that the warning or instruction was inadequate, you must decide whether this inadequacy was a cause of the injury. You should consider whether an adequate warning or instruction would have been read and followed and whether reading and following an adequate warning or instruction would have prevented Ms. Levine's injuries. As in the case of the negligence claim, you should bear in mind that the law does not require that an inadequate warning or instruction be the sole cause of the injury. Several factors may combine to cause an injury. The plaintiff is required to show that an inadequate warning or instruction was a substantial factor in causing her injury.

The defense of "intervening event" also applies to the strict liability claim. Wyeth has the burden on proof on this issue by a preponderance of the evidence. If you find that Wyeth has shown that the action of Ms. Fisch in continuing to administer Phrenegan to Ms. Levine after her complaint of plain was not foreseeable by Wyeth and that stopping the injection when Ms. Levine complained of pain would have prevented her injury, then you should find for Wyeth on the issue of causation.

You should reach a decision on your verdict form on both the issues of negligence and strict liability.

* * *

STATE OF VERMONT
COUNTY OF WASHINGTON, SS.

DIANA LEVINE

v.

Washington Superior Court
Docket No.: 670-12-01

AMERICAN HOME PRODUCTS, INC.
(Now WYETH).

Stamp: FILED
(initials)
MAR 12 2004
SUPERIOR COURT
WASHINGTON COUNTY

JURY VERDICT

I.. Negligence

1. Do you find that Wyeth was negligent in this case?

Yes √

No_____

If your answer is Yes, please continue to question 2. If your answer is No, please go directly to question 4.

2. Was the negligence of Wyeth a cause of Diane Levine's injuries?

Yes √

No_____

If your answer is Yes, please continue to question 3. If your answer is No, please go directly to question 4.

3. Did an "intervening cause" break the causal connection between Wyeth's negligence and Diana Levine's injuries?

Yes_____

No___√___

Now, go to question 4.

II. Strict Liability

4. Was the product Phenergan defective when administered to Diana Levine as a result of inadequate warning and instructions?

Yes___√___

No_____

If your answer is Yes, please continue to question 5. If your answer is No, please go to the instructions after question 6.

5. Were the inadequate warnings or instructions a cause of Ms. Levine's injuries?

Yes___√___

No_____

If your answer is Yes, please continue to question 6. If your answer is No, please go to the instructions after question 6.

6. Did an "intervening cause" break the causal connection between a defect in the product Phenergan and Ms. Levine's injuries?

Yes___√___ inadvertent checkmark (initials)

No √

Instructions

If you have answered Yes to questions 1 and 2 (and No to question 3), OR if you have answered Yes to questions 4 and 5 (and No to question 6), you should consider the issue of Damages.

Please state the amount of damages you award for the following elements of Ms. Levine's claim:

Economic losses and costs (Medical expenses, personal care and equipment costs, lost earnings and earning capacity	$ $2,400,000
Non-Economic losses (Personal injury damages)	$ $5,000,000

Dated: March 12, 2004

/s/
Foreperson

STATE OF VERMONT
WASHINGTON COUNTY, SS.

DIANA LEVINE	)	
	)	WASHINGTON SUPERIOR
v.	)	COURT
	)	DOCKET NO. 670-12-01 Wncv
WYETH	)	

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(initials)
SUPERIOR COURT
WASHINGTON COUNTY

JUDGMENT

This matter was tried before a jury, Honorable Geoffrey W. Crawford presiding, which rendered its verdict for the plaintiff, Diana Levine, on March 12, 2004. Based upon the verdict, the amount of an earlier settlement, and the parties' agreement for $74,000 in pre-judgment interest, it is Ordered and Adjudged that the plaintiff, Diana Levine, recover from the defendant, Wyeth, the sum of $6,700,000, plus $74,000 pre-judgment interest, for total of $6,774,000.

Dated at Montpelier, Vermont this 17th day of March, 2004.

/s/
Honorable Geoffrey W. Crawford

Approved as to form:

/s/ by (initials) with permission
Allan R. Keyes Esq.

STATE OF VERMONT
COUNTY OF WASHINGTON, SS.

DIANA LEVINE,
Plaintiff

v.

Washington Superior Court
Docket No.: 670-12-01

AMERICAN HOME
PRODUCTS, INC.
(Now Wyeth),
Defendant.

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SUPERIOR COURT
WASHINGTON COUNTY

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DECISION ON MOTION FOR JUDGMENT UNDER V.R.C.P. 50

This is a motion for judgment under Rule 50 following entry of judgment in a product liability case. The motion was timely filed and follows an earlier motion for judgment on the same grounds submitted at the close of the evidence.

Factual Background

This case arises out of an incident on April 7, 2000, when plaintiff received an injection of the drug Phenergan from physician's assistant Jessica Fisch at the Health Center in Plainfield, Vermont. Phenergan is an anti-nausea medication manufactured and sold by de-

fendant. As a result of the injection, plaintiff developed gangrene in her right hand. She underwent an amputation of her right arm at the elbow. Plaintiff settled a separate claim against the Health Center and her physician prior to suit.

The parties tried this case from March 8–March 11, 2004. The jury verdict was for $7,400,000. The parties stipulated to adjustments for the prior settlement and pre-judgment interest. The Court entered judgment on March 17, 2004, for $6,774,000.

Standard of Review

The standard of review for a Rule 50 motion is whether "during a trial by jury a party has been fully heard on an issue and there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue." V.R.C.P. 50(a). If the basis for the jury's verdict is insufficient, "the court may determine the issue against that party." *Id.* The trial court may grant the motion against a party "with respect to a claim or defense that cannot under the controlling law be maintained or defeated without a favorable finding on that issue." *Id.*; see also *Brueckner v. Norwich University*, 169 Vt. 118, 122 (1999) ("[A] trial court considers the evidence in the light most favorable to the nonmoving party, excluding the effect of any modifying evidence.") (citation omitted).

I. Federal Preemption by FDA approval of Phenergan labeling

Plaintiff's claim against defendant is based on allegations that defendant failed to warn of the hazards of intravenous injection of Phenergan. At trial plaintiff introduced evidence that Phenergan should be administered by intra-muscular injection or through a free-

flowing IV bag. Plaintiff's witnesses testified that injection into the patient's vein through a "butterfly" infusion set was too dangerous and should have been strongly discouraged in the instructions for use—the "package insert" or label which accompanies the product when it is provided to a physician.

Defendant argues that the approval of the Phenergan label by the Food and Drug Administration preempts Vermont product liability law on the issue of labeling and provides a defense as a matter of law to a claim based on failure-to-warn.

Factual Record at Trial

At trial defendant received wide latitude to introduce evidence about its interaction with the FDA concerning the Phenergan label. The factual record relevant to the Rule 50 motion is as follows:

1. The corrosive nature of Phenergan can lead to catastrophic tissue damage if it enters a patient's arterial blood flow. As the arteries become smaller and more diffuse, the tiny vessels can be damaged by exposure to Phenergan. The patient suffers spasm of the arteries, inflammation, loss of blood flow due to clotting, gangrene, and, in some cases, the loss of a limb or other serious injury. Green, Tr. 212, 216. Once Phenergan enters the arterial flow, there is no reliable way to reverse the harmful effects of the medication on the tiny vessels distal (downstream) from the site of the injection. Green Tr. 213.

2. In this case, plaintiff received an injection of Phenergan through the use of a "butterfly" intravenous infusion set. The butterfly set consists of a needle which is placed in the patient's vein and held in place by two flexible tabs—the "butterfly." The infusion set creates

a fixed point of entry into the vein. Medication can then be injected through the infusion set into the patient's vein. Alternatively, the infusion set can be hooked up to a free-flowing IV bag. Medication such as Phenergan can be added to the IV solution and administered through the IV drip. Matthews, Tr. 85-100. Ms. Fisch injected 50 milligrams of Phenergan directly through the butterfly infusion set into plaintiff's arm over the course of several minutes. She did not use a free-flowing IV bag. Matthews, Tr. 89-93.

3. For reasons that remain unclear, the Phenergan entered plaintiff's arterial system, either because the needle in the infusion set entered an artery directly or because the drug leaked out of the vein and entered an artery through a process called extravasation. Green Tr. 211. As a result of the injection, plaintiff suffered catastrophic injury to her right arm.

4. One way to reduce the risk of inadvertent intra-arterial injection is to set up a free-flowing IV bag and introduce the drug into the IV solution. This is an alternative to injection through the infusion set into a patient's vein. Administration through a free-flowing IV bag reduces the risk of inadvertent arterial injection because the nurse or physician can be more certain that the needle has been placed in a vein. A solution dripping from an IV bag will not flow freely into an artery due to back pressure from the patient. Green Tr. 194-98, 208-14.

5. The FDA has approved the label for Phenergan since at least 1974. Defendant Ex. P.

6. Since at least 1976, both the FDA and defendant have recognized that injection of Phenergan into an artery is dangerous and can result in severe injury. Defendant Ex. R. By 1976, the Phenergan label contained

specific warnings about the hazard of intra-arterial injection. Defendant Ex. S.

7. The minutes of an FDA anesthesiology advisory committee meeting on 10/14/76 include discussion of the Phenergan label then in use. The committee considered a variety of concerns including the risk of intra-arterial injection. The committee recommended that an additional warning should be added: "If a Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set." Ex. S.

8. In 1979, the FDA required extensive relabeling of pharmaceutical drugs, including Phenergan. The defendant gave some consideration to changing the warnings about intra-arterial injection to recommend use of an intravenous infusion set for administration of the drug. A 1981 proposed package insert contained the following language:

> When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

Ex. T. Defendant submitted the same proposed language to the FDA on 5/3/88 in conjunction with other proposed changes to the Phenergan label. Ex. M. The proposed language was never used.

9. In a letter to defendant dated 2/21/97, an FDA official directed defendant to "retain verbiage in current label" with respect to the risk of inadvertent intra-arterial injection. No warning or instruction concerning the preferred use of an intravenous infusion set appeared in the defendant's label, including the label in

use when the dose of Phenergan involved in this case was sold.

10. The letter dated 2/21/97 identifies the "current label" as the version which defendant submitted to the FDA by letter on 8/6/96. The defendant was unable to obtain a copy of the 8/6/96 letter until after the completion of the trial. The Court will accept and consider this post-trial filing as it relates to the issue of preemption. Preemption is an issue for the Court, not the jury. The post-trial filing removes an area of confusion identified by the Court in the summary judgment decision dated 12/23/03.

11. The 8/6/96 letter from defendant to the FDA contains minor revisions of an earlier label submitted in 1992. It confirms that in 1997, the FDA approved various label changes for Phenergan and rejected the language which defendant proposed in 1981 and 1988 concerning the preferred use of an intravenous infusion set for administering irritant drugs.

12. Plaintiff's expert witness Harold Green, M.D. testified that the warnings and instructions on the Phenergan label at the time of plaintiff's injury were inadequate to make the product safe because the defendant did not warn sufficiently of the risk of intravenous injection. Dr. Green testified that there was little medical justification for administration of Phenergan intravenously because of the availability of an intramuscular injection. If a physician chose intravenous administration of the drug, the use of a free-flowing IV bag would be safer than injection through a butterfly infusion set. Green Tr. 232-33.

13. Defendant's expert witness David Greenblatt, M.D. disagreed with Dr. Green. He testified that the clinician should remain free to decide whether to administer

Phenergan intravenously instead of by intramuscular injection. Greenblatt, Tr. 26-27. Dr. Greenblatt agreed with Dr. Green that it was safer to administer Phenergan through a free-flowing IV than by direct intravenous injection. Greenblatt, Tr. 49. Dr. Greenblatt testified that the butterfly infusion set could be considered to be a form of free-flowing IV administration. Greenblatt, Tr. 49.

Analysis

In any preemption case, the only issue is whether Congress intended to exercise the authority provided by the Supremacy Clause to serve as the exclusive source of law. U.S. Const. art. VI, cl. 2; see also M. Carrier, *Federal Preemption of Common Law Tort Awards by the Federal Food, Drug, and Cosmetic Act*, 51 Food & Drug L.J. 509, 510-11 (1996). In a system in which federal and state law frequently overlap and occupy the same ground, the Supreme Court has consistently required restraint from the lower courts in striking down state remedies. See, e.g., *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 249-57 (1984) (allowing state court imposed punitive damages against nuclear rod manufacturer despite extensive federal regulation over atomic energy). The issue is defined by and limited to the search for Congressional intent expressed in specific legislation. Preemption analysis does not depend upon whether a judge believes that federal regulation of conduct is preferable for reasons of consistency or greater technical expertise.

The starting point for any analysis is the basic assumption that Congress did not intend to displace state law in passing legislation. *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981). "Thus, while state action is preempted if it specifically frustrates the objectives, narrowly and

concretely defined, that underlie federal enactments, no such conclusion follows where the most that can be said is that the direction in which state law pushes someone's actions is in general tension with broad or abstract goals that may be attributed to various federal laws or programs." L. Tribe, American Constitutional Law 1187 (3d ed. 2000). The Supreme Court has stated that there is a strong presumption that "the historic police powers of the States [are] not to be superseded by Federal Act unless that [is] the clear and manifest purpose of Congress." *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218 (1947); but cf. *Hines v. Davidowitz*, 312 U.S. 52 (1941) (finding federal supremacy in the field of foreign affairs preempted a Pennsylvania statute requiring foreign aliens to register). In areas of health and safety, the U.S. Supreme Court has long recognized the primary interest of the states in the protection of their citizens. *Florida Lime & Avocado Growers v. Paul*, 373 U.S. 132, 144 (1963).

Congress has enacted preemption legislation in other related fields such as medical devices, 21 U.S.C. § 360k, and cigarette labeling, 15 U.S.C. § 1334, but it has not passed any legislation creating an area of *express* preemption for pharmaceutical labeling. See *Hurley v. Lederle Labs.*, 863 F.2d 1173, 1176 (5th Cir. 1988) (collecting decisions finding no express preemption for pharmaceutical labeling). When Congress has not enacted an express preemption provision, the courts must consider whether its intent to preempt state law can be fairly *implied*. The traditional bases for *implied* preemption are: (1) a comprehensive regulatory scheme which occupies the field so completely as to leave no room for state action (field preemption); (2) state law which obstructs the purpose of federal legislation (obstruction conflict preemption); or (3) a direct conflict

between state and federal law (direct conflict preemption). *Hillsborough County, Fla. v. Automated Medical Laboratories*, 471 U.S. 707, 713 (1985). Under this standard, defendants argue that the breadth of FDA activity and the potential for interference with its regulatory decisions creates a basis for *implied* preemption. The breadth of activity is a basis for a claim of *field* preemption. The potential for interference is a basis for claims of *conflict* preemption. The Court will address each separately.

Field Preemption

Since 1906, the Food and Drug Administration—then functioning as the Bureau of Chemistry—has reviewed and approved pharmaceutical labels under Congressional authority. 1906 Food and Drugs Act, ch. 3915, 34 Stat. 768 (repealed by the Federal Food, Drug, and Cosmetic Act of 1938, codified at 21 U.S.C. §§ 301 *et seq.* (2000)). The regulation of labeling is mandatory. Even minor changes require FDA approval. At the same time that the FDA has regulated pharmaceutical labels, plaintiffs in every state have filed tort claims against drug manufacturers on common law causes of action—principally strict liability for failure-to-warn. See, e.g., *McCallister v. Purdue Pharma L.P.*, 164 F. Supp. 2d 783, 787 (S.D. W. Va. 2001).

FDA regulation and state law tort remedies have coexisted for decades—generally to the consternation of the manufacturers. Despite countless "failure-to-warn" cases, filed over several decades, defendants have not identified an authoritative line of cases in which FDA regulation of pharmaceutical labels has been held to preempt the state law remedy of strict liability.

The evidence in this case demonstrates that FDA regulation of labeling is mandatory and comprehensive. It

has long operated in conjunction with state law tort claims. Both the Restatement (Second) and Restatement (Third) of Torts: Product Liability permit manufacturers to offer evidence of compliance with FDA requirements as evidence of lack of defect. Restatement (Third) of Torts: Product Liability § 4 (1998); Restatement, Second, of Torts § 288c. (1965). Compliance with the FDA regulations alone has never been held to be a bar as a matter of law to state law claims that a manufacturer failed to provide an adequate warning. Compare *Caraker v. Sandoz Pharmaceuticals Corp.*, 172 F. Supp. 2d 1018, 1030-39 (S.D. Ill. 2001), with *McCallister*, 164 F. Supp. 2d at 792-93 (noting some preemption implications of the Controlled Substances Act).

The absence of an express preemption provision in the enabling legislation for FDA regulation is strong evidence that Congress has chosen not to preempt state law remedies in the area of pharmaceutical labeling. Cf. *Jones v. Rath Packing Co.*, 430 U.S. 519, 537 (1977) ("If Congress had intended to overrule this longstanding ... practice, founded on a legislative statement of necessity, we would expect it to have done so clearly."); but cf. *Hurley*, 863 F.2d at 1179 (suggesting that the pervasiveness of FDA label regulations would preempt state action involving the adequacy of vaccines warnings). The *express* preemption provisions for medical devices, 21 U.S.C. § 360k, cigarettes 15 U.S.C. § 1334, and pesticides 7 U.S.C. § 136v(b), (FIFRA), demonstrate that Congress knows how to enact preemptive legislation when necessary. See *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 518-20 (1992) (interpreting express statutory preemption). These are obviously different than the implied preemption cases because Congress has spoken aloud and expressly on the issue.

The great majority of courts considering the issue have held that state law claims are not preempted by the dominant presence of the FDA in the field. See *Caraker*, 172 F.Supp. 2d at 1038-39; *Foyle v. Lederle Labs.*, 674 F.Supp 530, 533 (E.D.N.C. 1987); *Carlin v. Superior Court*, 920 P.2d 1347, 1352-53 (Cal. 1996); *Washington State Physicians Ins. Exch. & Assoc. v. Fisons Corp.*, 858 P.2d 1054, 1069 (Wash. 1993); *Feldman v. Lederle Labs*, 625 A.3d 1066, 1070 (N.J. 1993); *Plenger v. Alza Corp.*, 13 Cal.Rptr. 2d 811, 819 n.7 (1992); but see *Ehlis v. Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1197-98 (D.N.D. 2002) (dicta suggesting preemption through the medical device amendment might apply). The sheer number of these decisions demonstrates that this is not a new issue on which Congress has not had an opportunity to act.

The requirement that pharmaceutical labels be approved by the FDA is insufficient to overcome the presumption against implied preemption. This Court finds no basis for denying plaintiff her remedies under state law on the basis of field preemption.

Conflict Preemption—Obstruction

Whether state law damage claims actually impede the FDA in the pursuit of its mission is hard to see from the limited context of a single personal injury trial. Successive political administrations have differed on this issue. In 1998, the FDA posted its final version of new rules governing the labeling of prescription drugs and clarified that the rules did not in any way preempt tort liability or a manufacturer's duty to warn. *Prescription Drug Product Labeling; Medication Guide Requirements*, 63 Fed. Reg. 66378, 66383-84 (Dec. 1,1998). More recently, the FDA has had occasion to take the opposite position. Brief of Amicus Curiae

United States, *Motus v. Pfizer, Inc.*, 358 F.3d 659 (9th Cir. 2004) (Nos. 02-55372, 02-55498) (urging the court to affirm summary judgment because FDA regulations preempted plaintiff's duty to warn claim).

The perception of the administrative agency that its work is obstructed is not the standard at issue. Cf. *INS v. Cardoza-Fonseca*, 480 U.S. 421 (1987); *Chevron U.S.A., Inc. v. Nat. Resources Def. Council*, 467 U.S. 837 (1984) (rejecting outright deference to an agency's statutory interpretation in favor of an analysis of congressional intent and traditional statutory construction). It is only the intention of Congress that matters. See *Jones*, 430 U.S. at 525. Many agencies may believe that they possess comprehensive expertise in their field and that any requirement of law arising from another source interferes with their work.

Some tension between the FDA and common law tort remedies is natural, inevitable, and probably healthy. The two sources of law function to meet very different concerns. The tort process does not propose to provide policy and rules applicable to the entire pharmaceutical industry. Instead, it is concerned with compensating individuals for wrongs and providing pressure to curb negligent behavior and the sale of defective products. The FDA regulatory process does not propose to provide compensation in individual cases. Instead, it seeks to provide rules concerning testing, developing and labeling of pharmaceutical drugs which apply to all companies.

The record in this case does not indicate that the work of the FDA has been obstructed by the potential exposure of the manufacturer to state law tort liability. The evidence in this case is that a concern about inadvertent intra-arterial injection surfaced by 1979 and was

the subject of a relatively mild warning proposed by the defendant in 1981 and again in 1988. The FDA rejected the proposed labeling change 9 years later in 1997 in a brief comment. There is no evidence in this record that either the FDA or the manufacturer gave more than passing attention to the issue of whether to use an IV infusion to administer the drug. The proposed labeling change did not address the use of a free-flowing IV bag. Viewing the matter in hindsight through the lens of a single catastrophic case, this Court heard little evidence that the FDA reviewed the issue of the intravenous administration of Phenergan with scientific rigor or any sense of urgency.

This record is very different from the type of intensive regulation described by the Justice Department in their brief submitted in a May 2004 medical device case (*Horn v. Thoratec*). Ex. A to Wyeth's Memo dated 4/16/04. In that brief, the government described a comprehensive pre-market approval process for medical devices requiring an average of 1,200 hours of review time by the agency, thousands of pages of documentation, and substantial give-and-take between the agency and the manufacturer. Brief at p. 8, 21. According to the Justice Department, revision of an existing PMA follows an equally stringent and rigorous process. That is a very different process from the leisurely course of review for the Phenergan label changes conducted over some sixteen years. The regulatory process in this case was marked by long periods of dormancy and a conclusory decision in 1997 to require no change to the existing label. The recommendation of administration through a free-flowing IV bag never appears in the regulatory record. In short, a tort case is unlikely to obstruct the regulatory process when the record shows

that the FDA has paid very little attention to the issues raised by the parties at trial.

The principal basis for obstruction advanced by proponents of implied preemption in the pharmaceutical field is concern that excessive or unwarranted warnings will reduce the use of a safe and valuable medication. See Justice Department Brief in *Horn v. Thoratec* at 25-26; R. Pear, *In a Shift, Bush Moves to Block Medical Suits*, N.Y. Times, July 25, 2004, available at http://www.nytimes.com/2004/07/25/politics/25DRUG.html. The problem of "defensive warning" is not strong in this case. Any warning or instruction about the greater safety of a free-flowing IV bag relates only to the method of administration, not to the decision to use Phenergan. This case is different from cases involving proposed warnings of remote side effects which might dissuade physicians from using the drug to the detriment of the patient population.

There is no basis in this case to conclude that the work of the FDA was obstructed in any way by the indirect pressure of state law tort liability.

Conflict Preemption—Direct Conflict

The FDA regulations and a state law failure-to-warn case do not conflict directly. Compliance with the FDA labeling regulations is not a complete defense, but the manufacturer is entitled to raise it as a defense as defendant has done in this case. Restatement (Third) of Torts: Product Liability § 4. The record in this case is mixed concerning the ability of the defendant to provide a sharper warning about the risks of intravenous injection. While the defendant insisted that severe sanctions, including criminal prosecution, would follow any change to the label as approved by the FDA in 1981 and 1997, the FDA regulations permit strengthened

warnings without approval on an interim basis. 21 C.F.R. 314.70; see also *Kurer v. Parke, Davis & Co.*, 679 N.W. 2d 867, 872-74 (Wis. App. 2004).

More fundamentally, compliance with federal regulation does not provide a complete defense against tort liability. In a three-member partially dissenting opinion in *Cipollone v. Liggett Group*, 505 U.S. 504 (1992), Justice Blackmun wrote:

> The effect of tort law on a manufacturer's behavior is necessarily indirect. Although an award of damages by its very nature attaches additional consequences to the manufacturer's continued unlawful conduct, no particular course of action (*e.g.*, the adoption of a new warning label) is required. A manufacturer found liable on, for example, a failure-to-warn claim may respond in a number of ways. It may decide to accept damages awards as a cost of doing business and not alter its behavior in any way. Or, by contrast, it may choose to avoid future awards by dispensing warnings through a variety of alternative mechanisms, such as package inserts, public service advertisements, or general educational programs. The level of choice that a defendant retains in shaping its own behavior distinguishes the indirect regulatory effect of the common law from positive enactments such as statutes and administrative regulations. Moreover, tort law has an entirely separate function—compensating victims—that sets it apart from direct forms of regulation.

Id., 505 U.S. 536-37 (citations omitted). There is no direct conflict between the FDA regulatory process and

the common law remedy. The record in this case was that there have been at least 20 reports of amputations similar to plaintiff's injury since the 1960s. Green, Tr. 216. The defendant has remained in compliance with the FDA regulations by retaining the same warning about the risks of intra-arterial injection for several decades. This warning may be insufficient—certainly this jury found it to be so—and the result is that on some occasions the defendant may pay compensation. This tension does not amount to a direct conflict with the FDA labeling requirements. "The reason why many courts find no preemption is that the FDA's drug labeling decisions impose only 'minimum' standards that are open to supplementation by state law through a jury's verdict enforcing a manufacturer's common law duty to warn." *Caraker*, 172 F. Supp. 2d at 1033. The record in this case of a slow and imperfect regulatory process illustrates why courts have consistently held that FDA regulation provides a minimum standard of safety.

This Court finds no basis for federal preemption on grounds of direct conflict.

II. Causation

Defendant seeks to attribute sole causation as a matter of law to the actions of Jessica Fisch, P.A. who continued to inject the Phenergan despite a statement from the plaintiff that the injection hurt. This argument raises factual issues which were argued to the jury and resolved in plaintiff's favor at trial.

First, there is a factual dispute about whether it was too late for Ms. Fisch to stop the injection if the burning sensation experienced by the plaintiff was the Phenergan entering an artery. Second, the defendant requested and received a detailed instruction on effi-

cient intervening cause, which addressed the same issues raised in this motion. Third, and most importantly, warnings are almost never the *sole* cause of an injury. Injury occurs only after the warning combines with human conduct to produce at least two concurrent causes of the event. *Gilman v. Towmotor Corp.*, 160 Vt. 116, 119-20 (1992); see also Restatement (Third) of Torts: Product Liability § 2 cmt. m (foreseeability); *id.* at § 16 (increased harm due to product defect). The warning is read—or not—by some human actor who follows it—or not. If subsequent human action were enough to break the chain of causation, there would be no cause of action for failure-to-warn. Restatement (Third) of Torts: Product Liability § 17.

The plaintiff's claim is not that Ms. Fisch was without blame or fault. Rather, as this Court understands it from trial, the claim is that if Ms. Fisch and her supervising physician had been told of the risk of limb death and amputation, she would have administered Phenegan by a safer method than the butterfly infusion set. In rejecting the defense of efficient intervening cause, the jury decided that any conduct by Ms. Fisch did not break the chain of causation. There is sufficient evidence from Ms. Fisch, Dr. Matthews, and Dr. Green to support the jury's conclusion. This evidence is principally the testimony from Dr. Matthews that he would never have permitted administration of Phenergan through direct injection at his clinic if he had known of the risks to the patient and the testimony from Dr. Green that use of a free-flowing IV bag or intramuscular injection are safer methods of administering the drug.

Plaintiff argued at trial that a safer method of administration would have greatly reduced the risk of injury from inadvertent arterial injection. The defendant ar-

gued that injection through the butterfly-infusion set remains an appropriate method of administration. The jury rejected this defense and accepted the plaintiff's version of the facts. The Court will not overturn the verdict on a factual issue when there is evidence to support the jury's conclusion.

III. Damages

Defendant seeks a new trial for damages on the grounds that the Court did not grant a present value instruction for general damages (non-economic damages), which resulted in an oversized general damages award ($5,000,000). No challenge is raised to the award of special damages (medical and rehabilitative expenses and lost income) in the amount of $ 2.4 million.

A. Present Value Instruction

In this case, the Court rejected defendant's request for an instruction that any award of future general damages should be reduced to present value. There were several reasons for this.

First, the defendant put on no proof or argument concerning how to reduce future pain and suffering to present value. Nor, of course, did plaintiff. Future *economic* damages were always reduced to present value by plaintiff's economist and were essentially conceded without challenge by defendant. See, e.g., *Girroir v. Carpenter*, 136 Vt. 290, 292 (1978); *Wolfe v. Mendel*, 84 N.W.2d 109, 111, 115 (Neb. 1957) ("Where an instruction does not prohibit or negative the computation of damages upon the basis of their present worth, it will not be assumed that the jury did not understand that it was to estimate the present value of future earnings lost."). The defense never proposed a method by which the jury could discount for prevailing interest rates

while accounting for the effects of expected inflation. Even the 12 % discount rate proposed in the post-trial briefs was not suggested.

The briefing on this motion illustrates the practical difficulties of instructing the jury in a meaningful fashion that they should reduce the award of future pain and suffering to present value. The lawyers have presented wildly different proposals and methodologies. The defendant proposes a simple discount rate based on 12 % or 2 %. It offered no economic opinion at trial.

On the evidentiary record alone, including closing arguments, there was an inadequate basis for a present value instruction on future pain and suffering.

Second, the majority view—starting with the Restatement (Second) of Torts § 913A cmt. a—is that the calculation of future general damages is too subjective to be subjected to economic analysis by a lay jury. *Flanigan v. Burlington N., Inc.*, 632 F.2d 880, 886 (8th Cir.1980); *O'Byrne v. St. Louis Southwestern Ry. Co.*, 632 F.2d 1285, 1286 (5th Cir.1980); *Taylor v. Denver & Rio Grande W. R.R.*, 438 F.2d 351, 353 (10th Cir.1971) ("[T]he courts [have] held that the better reasoned authority supports the rule that future pain and suffering should not be reduced to current worth."); *United States v. Harue Hayashi*, 282 F.2d 599, 605-06 (9th Cir.1960); *Texas & Pacific Railway Co. v. Buckles*, 232 F.2d 257, 264 (5th Cir. 1956); *Chicago & N.W. Ry. Co. v. Candler*, 283 F. 881, 885 (8th Cir. 1922) ("The arbitrariness and artificiality of such a method is so apparent that to require a jury to apply it would, we think, be an absurdity."); *Purdy v. Belcher Refining Co.*, 781 F.Supp. 1559, 1563 (S.D.Ala.1992); *Hanson v. Reiss Steamship Company*, 184 F.Supp. 545, 552-53 (D.Del.1960) (holding that allowances for future pain

and suffering are not subject to reduction to present worth); *Sleeman v. Chesapeake & O. Ry. Co.*, 305 F.Supp. 33, 36 n.1 (W.D.Mich. Sep 09, 1969) vacated, 424 F.2d 547 (6th Cir. 1970); *Schirra v. Delaware, L. & W.R. Co.*, 103 F.Supp. 812, 824 (M.D.Pa.1952); *Beaulieu v. Elliott*, 434 P.2d 665, 671-72, 676 (Alaska 1967); *Braddock v. Seaboard Air Line R.R.*, 80 So.2d 662, 666-68 (Fla.1955); *Delva v. Value Rent-A-Car*, 693 So.2d 574, 578 (Fla.App. 1997); *Bagley v. Akins*, 138 S.E.2d 430, 431 (Ga.App. 1964); *Brant v. Bockholt*, 532 N.W.2d 801, 803-04 (Iowa 1995) (collecting cases); *Louisville & N.R. Co. v. Gayle*, 263 S.W. 763 (Ky. 1924); *Busch v. Busch Const., Inc.*, 262 N.W.2d 377, 397 (Minn. 1977); *Barlage v. The Place, Inc.*, 277 N.W.2d 193, 195 (Minn.Sup.Ct. 1979); *Dickerson v. St. Louis S.W. Ry.*, 697 S.W.2d 210, 212 (Mo.App.1985); *Ball v. Burlington N. R.R.*, 672 S.W.2d 358, 361 (Mo.App.1984); *Porter v. Funkhouser*, 382 P.2d 216, 218-19 (Nev. 1963); *Friedman v. C & S Car Serv.*, 527 A.2d 871, 873-75 (N.J. 1987); *Bready v. Tipton*, 407 P.2d 194, 206 (Okla. 1965); *Yost v. West Penn. Ry Co.*, 9 A.2d 368, 369-70 (Pa. 1939); *Missouri Pac. R.R. v. Handley*, 341 S.W.2d 203, 205 (Tex.Civ.App. 1960); *Borzea v. Anselmi*, 258 P.2d 796, 804 (Wyo. 1952); 22 Am. Jur. 2d *Damages* § 999 ("[T]he generally accepted rule is that the award [for pain and suffering] is not to be thus reduced [to present worth]."); see also *Oliveri v. Delta S.S. Lines, Inc.*, 849 F.2d 742, 750-52 (2d Cir. 1988) (noting that the majority of state jurisdictions do not reduce future pain and suffering awards and criticizing the rule requiring reduction to present value); *Hogan v. Santa Fe Trail Transportation Co.*, 85 P.2d 28, 34-38 (Kan. 1938) (Wedell, J., dissenting) (collecting early cases); *McKenna v. State*, 492 N.Y.S.2d 805, 807 (1985).

Third, it would involve the Court and the jury in something of a charade to pretend that without expert guidance, the jurors are capable of running accurate present value calculations on general damage awards proposed during deliberations. Judges and lawyers are universally incapable of performing the discount calculations with or without a calculator and the tables of historic interest rates and inflationary factors. It is invariably the topic of expert testimony by an economist, and then only on the elements of special damage such as lost income and future medical bills. As Professor Dobbs succinctly states the issue:

> The Rule requiring reduction to present value must be qualified in several ways. In the first place, viewed realistically, the plaintiff is often not required to put on proof or explanation how reduction is to take place, and if the jury only gets an instruction to make the reduction without any further explanation, the rule probably does not mean very much. Beyond this, there is the agreed limit to the rule that only pecuniary losses are reduced. Thus awards for future pain and suffering, or for the future loss of companionship or guidance, are made without reduction. Presumably this is because it would be futile and even misleading to compute mathematically a reduction on an award that could have no mathematical basis in the first place.

D. Dobbs, *Handbook on the Law of Remedies* § 8.7, at 574 (1st ed. 1973).

For this reason, the Vermont Supreme Court has limited *pre-judgment* interest to special damages. *Gilman*, 160 Vt. at 121; see also *Bull v. Pinkham Eng'g*

Assoc., 170 Vt. 450, 463-64 (2000); *Ulm v. FordMotor Co.*, 170 Vt. 281, 292-94 (2000); *Remes v. Nordic Group, Inc.*, 169 Vt. 37, 40-41 (1999); *Estate of Fleming v. Nicholson*, 168 Vt. 495, 501-03 (1998); *Winey v. William E. Dailey, Inc.*, 161 Vt. 129, 141 (1993); *Turcotte v. Estate of LaRose*, 153 Vt. 196, 198-200 (1989). It would be uneven at best to eliminate pre-judgment interest on general damages while requiring a reduction for future awards. Cf. Restatement (Second) of Torts § 913A cmt. a (linking present worth valuations with § 912 and its prohibition on prejudgment interest for pain and suffering). The reasoning that it is

The Court will not grant a new trial on the basis of the jury charge on general damages.

B. Reasonableness of the general damage award

Defendant cites several Vermont verdicts ranging from $1 million to $3 million recorded between 1977 and 1999. Defendant argues that at $5 million for general damages, this verdict is too high. Defendant does not take issue with the award of $2.4 for special damages and did not challenge the proof on that issue at trial.

This Court will not remit or set aside the damages verdict because the damage award is reasonably supported by the proof at trial. *Dean v. Arena*, 141 Vt. 647, 650 (1981). Several factors support a high award for pain and suffering.

First, this was an extraordinary case. The defendant describes it as tragic, and the Court saw it the same way at trial. The proof of plaintiff's joy and commitment to music prior to the loss of her arm was very compelling. The immediate effects of the injury were horrific. The changes in plaintiff's life as a result of her injury are wide and deep. This was as bad an injury

case as any court is likely to see. What made the case unusual was the way that the injury cut so directly into the life of a musician. The evidence of plaintiff's suffering and the loss of her ability to play the guitar at a professional level was powerful and undisputed.

Second, the jury verdicts presented by defendant place this verdict at one end of a range of results in serious cases in Vermont. So far as it is possible to tell, this jury verdict is the largest to date in a personal injury case. The verdicts are necessarily incomplete because they do not include settlements. This information is available only at third-hand, but it is generally known within the Vermont legal community; over the course of the last 10 years, a few severe injury cases have settled for amounts in excess of the verdicts listed by defendant. In October 2002, the Lamoille Superior Court entered judgment in a case involving quadriplegia for $48,000,000 following a bench trial. *Perron v. Vt. Utility Serv. Inc.*, No. 154-8-01LeCv (Cashman, J., Oct. 2002). On April 8, 2004, the Addison Superior Court entered judgment for $2,345,764 after a damages hearing in a default case concerning a severe foot injury. *Hadvab v. Manning*, No. 121-6-03 Ancv, 8 Vt.TrialCt.Rep. 274 (Toor, J.). This Court does not rely on these results in any direct evidentiary fashion because the underlying facts are not available for comparison, but they do provide some indication that a $7.4 million dollar verdict is not an isolated event within our legal culture.

The standard for review of a damages award is whether the award is "entirely excessive" or "shocks the conscience." *Turgeon v. Schneider*, 150 Vt. 268, 274 (1988); *Newhall v. Central Vermont Hospital*, 133 Vt. 572,576-77 (1975). This was a bad damages case. The defendant chose not to challenge the damages at trial. The verdict

falls within a range of results seen in recent years in our state. This Court finds that the verdict is reasonably supported by the evidence and is not excessive for purposes of Rule 50 or Rule 59(a).

CONCLUSION

Defendant's motion for judgment under Rule 50 or, in the alternative, for a new trial on damages is DENIED.

Dated: 7-30-04

/s/_____
Superior Court Judge

STATE OF VERMONT

WASHINGTON COUNTY, S.S.

LEVINE)

-v-)

WYETH)

TAPED HEARING

-before-

THE VERMONT SUPREME COURT

Taken on October 5, 2005

Supreme Court Building

Montpelier, Vermont.

* * *

[7] [MR. REIN] supremacy clause of the constitution. This issue is raised below in several times and it was adjudicated as a matter of law, and it's properly before this Court for de novo review as a matter of law.

I want to emphasize to the Court that issue as presented here is very narrow and very particularized. It's what is called a conflict preemption issue, a collision between state and federal requirements on the specific labeling of Phenergan. It's focused on Phenergan in the facts of this case. Wyeth is not contending for a field preemption, for the ouster of Vermont law, tort law,

not at issue here. Wyeth is not contending that the mere compliance with the federal—

FEMALE JUSTICE: You have briefed those issues, so I want to make sure I understand, you are no longer contending field preemption?

MR. [REIN]: We did brief them below but not in this Court. This is conflict preemption, not field preemption. We have said that the background of intense federal regulations lends weight to the conflict preemption. We are not arguing for conflict preemption nor are we arguing that the mere compliance with the federal labeling requirements in and of itself creates a conflict preemption, contending on the specific duties at issue here.

[8] Um, and so the question the Court must focus on is where is the conflict? What are we talking about? And let's put it as simply as possible. Vermont law as formed and applied at the trial Imposed on Wyeth a labeling duty, a duty to label in a particular way which in our view and in our brief would have shown would have forced Wyeth to commit a prohibited act under federal law. And even if you assume that it wasn't a prohibited act, would have required Wyeth to take an action which would have frustrated the objects and purposes of FDA regulation.

* * *

[10] says that [Geier] is overruled or that [Cipollone] is overruled and [Cipollone] is the smoking case where the Supreme Court first said: "A duty imposed by state law, albeit through the tort system, is a duty which has to be judged in conflict preemption. And Bates really turned on statutory preemption because there is statutory language in Bates which was put at

issue, very similar to the medical device amendment, so it's a slightly different case. And so—

MALE JUSTICE: If I can interrupt. So what procedure or course would your client have had with regard to FDA upon a denial, as you've characterized it, of the CBE, the change in the notice, to get out of the box, so to speak, administratively?

MR. [REIN]: I think that really gets to the heart of the matter. You have to ask where our client was. What we were being told in the plaintiff's brief was that Wyeth was negligent, and I'm quoting from page 11, "because the label failed to instruct that any IV administration be through a free-flowing IV system or not at all." So that was the duty that was imposed by Vermont law at the plaintiff's request.

From a federal point of view, Wyeth submitted a supplemental application to the FDA which was ruled on by the FDA in 1997, and when the FDA ruled on it, they said,

* * *

[17] [MR. RUBIN] role to play in protecting its citizens in health and safety. There is a presumption against preemption, and a particular presumption against it in cases like this.

So what do they have to prove? They have to prove by clear evidence that a conflict is irreconcilable and it is impossible for Wyeth to both comply with the label and comply with Vermont common law that safe drugs be given to patients in Vermont.

FEMALE JUSTICE: But what about the argument that what is different in this case is that they asked to change the label and the FDA issues this language that says retain verbiage on the current label or

retain current verbiage or something like that. Does that make a difference from all those other cases?

MR. [RUBIN]: No, it doesn't, because what our case was essentially is quite simple. This drug is safe if it's injected intramuscularly. Four witnesses testified, Do not inject Phenergan IV push. Do not push it directly into a vein. That was the instruction that we wanted and that was the instruction that the jury found was necessary. So let's look at what in fact the FDA rejected. The first instruction says when administrating any irritant drug intravenously, it's usually preferable to inject (unclear) et cetera, et cetera. There is nothing in this language which precludes IV push. This

* * *

[21] method of administration of drugs or just to the—

MR. [RUBIN]: No. I think it's misrepresenting that the drug—

FEMALE JUSTICE: —elements of the drug itself, or the usefulness or the drug itself. Is there any distinction to be made there?

MR. [RUBIN]: Yeah. I think misbranding is that drug will do something that it can't do or be used for something that it shouldn't be used for. But if they want a conflict preemption here, they need a document, and you look at this document here, it's from the FDA and they say we considered the IV push method of injection. We think that you must include the option of IV push in your label because we believe that the patients who get your drugs should have that option. That is what they need, something like that. That would be clear evidence of a conflict.

As both trial judges said in this case, there is nothing in the record. What they have is a letter that says use the current verbiage. That is the record.

MALE JUSTICE: What about the argument, it's not just enhancing the safety warning, but in effect it's removing from professional availability a procedure, however risky, which had been recognized as available? You know.

LETTER FROM FDA TO WYETH DATED AUGUST 26, 1955 (DEFENDANT'S SUMMARY JUDGMENT EXHIBIT B)

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON 25, D. C.

Stamp: AUG 26 1955

NDA 8857

Wyeth Laboratories, Inc.
Attention: Dr. Ashkenaz
1401 Walnut Street
Philadelphia, Pa.

Gentlemen:

This will acknowledge your communications of July 5, 1955, July 8, 1955 and July 29, 1955, submitting additional material pertinent to your new drug application 8857 for your product "Injection Phenergan Hydrochloride".

It is understood as discussed with your representative Dr. Ashkenaz in person on June 21, 1955 and by telephone on August 22, 1955 that translations of the various French articles will be submitted to complete the requirements under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act.

It is understood as discussed with Dr. Ashkenaz by telephone on July 5, 1955 that the second sentence of the first paragraph under "Indications" in the revised brochure will be changed to read as follows: "Injection

Phenergan Hydrochloride' has also proven useful as a sedative particularly when used as preanesthetic medication". This involves deletion of the references to "prevention of post-operative nausea and vomiting" and to "use with meperidine and chlorpromazine in hibernation anesthesia".

We are taking action on this application with the understanding that these things will be done.

We have completed our study of this application and in accordance with the provisions of the regulation under section 505(c) of the Act it has become effective.

Please submit five copies of the final printed label and labeling and three finished market packages of the drug when available.

Sincerely your,

/s/

Barbara Moulton, M.D.
Medical Officer
New Drug Branch
Division of Medicine

INTERNAL WYETH MEMORANDUM DATED FEBRUARY 17, 1967 (PLAINTIFF'S SUMMARY JUDGMENT EXHIBIT 15)

INTERNAL CORRESPONDENCE

[logo]

to William E. Langeland, Ph.D.	from Walter H. Comer, M. D.
company W L D located Radnor	company W L D located Radnor
subject Phenergan® Adverse Reaction	date February 17, 1967

Lt. Colonel Harry Cerha
Headquarters, AFMSTC
Washington, D.C. 20333

Dear Bill:

Lt. Colonel Harry Cerha informed us of an adverse reaction occurring in a woman during labor involving three drugs given intravenously in a single injection. These drugs are Demerol®, Leritine® and Phenergan. A severe arteriospasm resulted during the injection, acceptable treatment, the spasm continued, resulting in gangrene of the arm and subsequent amputation.

The information from Colonel Cerha was given in a phone conversation February 15, 1967, and is not complete. The incident occurred some time in 1965. This information is being presented to the Food and Drug Administration because it is the first such incident reported to us involving Phenergan.

Phenergan was given (50 mg.) IV in a dose not recommended in the approved Phenergan direction circu-

lar. The direction circular also gives warning against perivascular extravasation and also includes a warning against intra-arterial injection.

Information reached us because of an allegation on the part of the patient against the Air Force.

Sincerely,

/s/

Walter H. Comer, M. D.

WHC:jda

Enclosure—Drug Reaction Report

cc: Mr. Smythe
Mr. Deuble
Dr. Shaw
Medical Routing
File

[illegible stamp]

[logo]

LETTER FROM FDA TO WYETH DATED AUGUST 5, 1974 (DEFENDANT'S TRIAL EXHIBIT P)

[logo]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 8-857/S-003

Stamp: AUG 5 1974

Stamp: RECEIVED
AUG 8 1974
[illegible]

Wyeth Laboratories, Incorporated
Attention: W. E. Langeland, Ph.D.
P.O. Box 8299
Philadelphia, Pennsylvania 19101

Gentlemen:

We acknowledge the receipt on March 26, 1974, of your communication dated March 19, 1974, regarding your supplemental new drug application of December 18, 1973, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenergan (promethazine hydrochloride) Injection.

The supplemental application provides for revised labeling.

We have completed the review of this submission and conclude that convulsions can occur with therapeutic doses of phenothiazines so it would be misleading to list this reaction only under the overdosage section in association with suicide attempts. We also recommend the following changes in the "Revised July 26, 1973" package insert:

Under the heading Actions; delete the words "that has" and insert "with the", and add the phrase "characteristics of this class of drugs." Also, delete the phrases "which is of marked potency and prolonged duration" and "so that it is useful in a variety of clinical situations."

Under the heading Warnings, change the first sentence in the third paragraph to: "The intravenous use of promethazine is not without hazard." In addition, add the sentence/paragraph: "The safety of Phenergan in women who are or may become pregnant has not been established; hence it should be given only when the potential benefits have been weighed against the possible hazards to mother and child."

Under the heading Adverse Reactions, change the first sentence in the second paragraph to: "Cases have been reported where patients receiving promethazine have developed leukopenia, and agranulcytosis". The next sentence should read: "In nearly every instance reported other toxic agents have been associated with the administration of promethazine. The third paragraph first sentence should be revised to: "Cardiovascular side-effects from promethazine have occurred. The phrase "although extremely rare" should be deleted from

the first sentence of the fourth paragraph. The word "rarely should be deleted from the first sentence of the fifth paragraph and the phrase "and convulsions", should be added to the end of the sixth or last paragraph.

Please let us know promptly your proposal in regard to the above recommendations.

Sincerely yours,

/s/

Barrett Scoville, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Scientific Evaluation
Bureau of Drugs

LETTER FROM WYETH TO FDA DATED DECEMBER 23, 1974 (DEFENDANT'S TRIAL EXHIBIT Q)

WYETH LABORATORIES INC. [logo] *Box 8299 , Philadelphia, Pennsylvania, 19101*

December 23, 1974

NDA 8-857/S-003

Barrett Scoville, M.D., Acting Director
Division of Neuropharmacological Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Scoville:

Reference is made to our approved new drug application (NDA 8-857) for "Phenergan®, promethazine hydrochloride, Injection" and to your letter of August 5, 1974 regarding the package insert for this product.

We are pleased to provide herewith draft copy of this package insert for this product revised in accordance with the recommendations contained in your above referenced letter of August 5, 1974.

We trust that you will find these revisions satisfactory and will so inform us at your earliest convenience.

Sincerely,

WYETH LABORATORIES INC.

William E. Langeland, Ph. D.
Director, Project Coordination
Division

PVU:[illegible]
Encs.

cc: Dr. Bogash
Dr. Comer
Dr. Force
Dr. Gold
Dr. Lewis
Mr. McCarthy
Dr. Shaw
Mr. Smythe
Mr. Swenson
Mr. Welker

BEST AVAILABLE COPY

A.H.F.S. Category 4:00, 28:24, 68:20

Wyeth
Phenergan®
(promethazine hcl)
Injection

Description
Each cc. of injection contains either 25 mg. or 50 mg. promethazine hydrochloride with 0.1 mg. disodium edetate, 0.04 mg. calcium chloride and not more than 0.25 mg. sodium metabisulfite and 5 mg. phenol with sodium acetate buffer.

ACTIONS

Phenergan is a phenothiazine derivative with the characteristics of this class of drugs. In addition to its antihistaminic action it also provides antiemetic as well as sedative actions.

Indications
The injectable form of promethazine hydrochloride is indicated for the following conditions when use of the oral form is impractical:
Amelioration and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions.
In anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
Active treatment of motion sickness.
Preoperative, postoperative and obstetric (during labor) sedation.
Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
As an adjunct to analgesics for the control of postoperative pain.
For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery, and poor risk patients, with reduced amounts of meperidine as an adjunct to anesthesia and analgesia.

Contraindications
Phenergan is contraindicated in individuals with a known hypersensitivity to the drug.
Under no circumstances should promethazine hydrochloride be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene.

Warnings
The sedative action of promethazine hydrochloride is additive to the sedative effects of central nervous system depressants; therefore, agents such as alcohol, barbiturates and narcotic analgesics should either be eliminated or given in reduced dosage in the presence of promethazine hydrochloride. When given concomitantly with promethazine hydrochloride the dose of barbiturates should be reduced by at least one-half and the dose of analgesic depressants, such as meperidine or morphine, should be reduced by one-quarter to one-half.

The preferred parenteral route of administration is by intramuscular injection. Subcutaneous injection is not recommended; evidence of chemical irritation has been noted and necrotic lesions have resulted on rare occasions following subcutaneous injection.

The intravenous use of promethazine is not without hazard.

Due to the close proximity of arteries and veins in the area most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. In such cases chemical irritation may be severe and spasm of digital vessels with resulting gangrene requiring amputation is a possibility.

When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg per cc. and at a rate not to exceed 25 mg. per minute.

The safety of Phenergan in women who are or may become pregnant has not been established; hence it should be given only when the potential benefits have been weighed against possible hazards to mother and child.

Precautions

Ambulatory patients should be cautioned against driving automobiles or operating dangerous machinery until it is known that they do not become drowsy or dizzy from promethazine hydrochloride therapy.

Antiemetics may mask the symptoms of an unrecognized disease and thereby interfere with diagnosis.

Patients in pain who have received inadequate or no analgesia have been noted to develop "athetoid-like" movements of the upper extremities following the parenteral administration of promethazine. These symptoms usually disappear upon adequate control of the pain.

Adverse Reactions

Patients may occasionally complain of autonomic reactions such as dryness of the mouth, blurring of vision and, rarely, dizziness.

Cases have been reported where patients receiving promethazine have developed leukopenia and agranulocytosis. In nearly every instance reported other toxic agents have been associated with the administration of promethazine.

Cardiovascular side-effects from promethazine have occurred.

Minor increases in blood pressure and occasional mild hypotension have been reported.

Photosensitivity has been reported.

Occurrence of photosensitivity may be a contraindication to further treatment with promethazine or related drugs.

Attempted suicides with promethazine have resulted in deep sedation, coma, rarely convulsions and cardiorespiratory symptoms corresponding with the depth of sedation present. A paradoxical reaction has been reported in children receiving a single dose of 25 mg. to 50 mg., characterized by hyperexcitability and abnormal movements. Nightmares and respiratory depression have also been reported.

As with other phenothiazine drugs the following adverse reactions have been reported: extrapyramidal reactions (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, parkinsonism) and convulsions.

Dosage and Administration

The preferred parenteral route of administration is by intramuscular injection. The proper intravenous administration of promethazine hydrochloride is well tolerated, but use of this route is not without some hazard; subcutaneous injection is not recommended (see Warnings).

ALLERGY: When the oral route is not feasible Phenergan® given intramuscularly or intravenously may be used. The average dose is 25 mg. The dose may be repeated within two hours if necessary, but oral therapy should be resumed if indicated and existing circumstances permit.

For children, single 25 mg. doses at bedtime or 6.25 to 12.5 mg. doses three times daily will usually suffice. After initiation of treatment in children or adults, dosage should be adjusted to the smallest amount adequate to relieve symptoms.

The administration of promethazine hydrochloride in 25 mg. doses prior to or during blood transfusion will prevent or control minor transfusion reactions of an allergic nature.

MOTION SICKNESS: The average adult dose for the active treatment of motion sickness is 25 mg. When oral medication cannot be tolerated, the dose should be given intravenously or intramuscularly. 12.5 to 25 mg. doses may be repeated as necessary at four to six hour intervals.

NAUSEA AND VOMITING: The average effective dose of Phenergan for the active therapy of nausea and vomiting associated with certain types of anesthesia and surgery is 25 mg. When oral medication cannot be tolerated, the dose should be given intravenously or intramuscularly. 12.5 to 25 mg. doses may be repeated as necessary at four to six hour intervals.

For prophylaxis of nausea and vomiting, as during surgery and the postoperative period, the average dose is 25 mg. repeated at four to six hour intervals as necessary.

For nausea and vomiting in children the dose should be adjusted to the age and weight of the patient and the severity of the condition being treated.

SEDATION: This product relieves apprehension and induces a quiet sleep from which the patient can be easily aroused. Administration of 12.5 to 25 mg. Phenergan at bedtime will promote sedation in children. Adults usually require 25 to 50 mg. for nighttime, preoperative or obstetrical sedation.

PRE AND POST OPERATIVE USE: Phenergan in 12.5 to 25 mg. doses for children and 50 mg. doses for adults the night before surgery relieves apprehension and produces a quiet sleep.

For preoperative premedication, children require doses of 0.5 mg. per pound of body weight in combination with an equal dose of meperidine and the appropriate dose of an atropine-like drug. Usual adult dosage is 50 mg. Phenergan with an equal amount of meperidine and the required amount of a belladonna alkaloid

For postoperative sedation and adjunctive use with analgesics, the dose is 12.5 to 25 mg. in children and 25 to 50 mg. in adults.

OBSTETRICS. Phenergan in doses of 50 mg. will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, administer 25 to 75 mg. (average dose 50 mg.) promethazine hydrochloride intramuscularly or intravenously with 25 to 75 mg. meperidine (average dose 50 mg.). Amnesic agents may be administered as necessary. If the average doses of Phenergan and meperidine are used, it is seldom necessary to repeat the medication during a normal labor. If necessary, 25 to 50 mg. doses, with or without a reduced dose of analgesic, may be repeated once or twice, at three to four hour intervals.

How Supplied

Phenergan® (promethazine hydrochloride) Injection, 25 and 50 mg., is available in Ampuls of 1 cc.

Wyeth Laboratories Inc., Philadelphia, Pa. 19101
Printed U.S.A.

December 20, 1974

LETTER FROM FDA TO WYETH DATED MAY 4, 1976 (DEFENDANT'S TRIAL EXHIBIT R)

[illegible handwriting]

pc: Dr. Bogash
Dr. Gold
Dr. Langelan
Mr. Ross
Dr. Shaw
Mr. Smythe
Mr. Swenson

[logo]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 8-857/S-005

Stamp: MAY 04 1976

Stamp: RECEIVED
May 7 1976
[illegible]

Stamp: RECEIVED
May 10 1976
[illegible]]

Wyeth Laboratories
Attention: Earl T. Lewis, M.D.
P. O. Box 8299
Philadelphia, Pennsylvania 19101

Gentlemen:

Reference is made to your supplemental new drug application of November 14, 1975 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for PHENERGAN(R) (promethazine hydrochloride) Injection.

The supplemental application provides for a revised package insert as discussed in our conference of August 25, 1975 and in our letter of August 29, 1975.

We have completed review of this supplemental application as submitted with draft labeling. In order to furnish adequate information for the safe use of the drug, the following revisions in the labeling should be made:

A. DESCRIPTION:

The structural formula of the drug should preceed the text material in this section.

B. INDICATIONS:

The last line of number 9 in this section should be rephrased to read "reduced amounts of meperidine or other narcotic as an adjunct to anesthesia and analgesia."

C. CONTRAINDICATIONS:

1. In the first paragraph the word "and" following the statements in parentheses should be deleted, a comma inserted and the following phrase added, "in patients who have bone marrow depression" so that the paragraph will now read as follows "Promethazine is contraindicated in comatose states, in patients who have received large amounts of central nervous system

depressants (alcohol, barbiturates, narcotics, etc.), in patients who have bone marrow depression and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine."

2. Since arterial injection is not an acceptable means of administering drugs, the second paragraph should be deleted.

D. WARNINGS:

1. In the paragraph entitled "Usage in Pregnancy," the following sentence should be added: "Jaundice and hyperreflexia have been reported in infants whose mothers received phenothiazines during pregnancy."

2. In the paragraph entitled "USAGE IN CHILDREN," the following sentence should be added: "Promethazine or any phenothiazine, used for symptomatic relief of nausea and vomiting associated with viral diseases, may mask early signs of developing central nervous system involvement, such as Reye's Syndrome."

3. The paragraph entitled "USE IN THE ELDERLY" should be modified by adding the following statement as a second sentence: "Because of reduced therapeutic requirements, dosage should be reduced accordingly."

4. After the "USE IN THE ELDERLY" paragraph, insert the following paragraph: "Promethazine should be used with extreme caution in patients with:

asthmatic attack

narrow angle glaucoma
prostatic hypertrophy
stenosing peptic ulcer
pyloroduodenal obstruction
bladder neck obstruction
patients receiving monoamine oxidase inhibitors"

5. The last paragraph as it appears on page three of the draft labeling should be modified as follows: the statement "when used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg per cc, and at a rate not to exceed 25 mg per minute," should be deleted and removed to the DOSAGE AND ADMINISTRATION section. Preceeding the remainder of the paragraph the following statement should appear, all in caps: "ASPIRATION OF DARK BLOOD DOES NOT PRECLUDE INTRA-ARTERIAL NEEDLE PLACEMENT AS BLOOD IS DISCOLORED UPON CONTACT WITH PROMETHAZINE." The remainder of the paragraph is acceptable.

E. PRECAUTIONS:

1. In the first paragraph, 4th line, the word "by" should be changed to "to" so that the sentence will read: "The dose of a narcotic or a barbiturate should be reduced to 1/4 to 1/2 the usual amount when promethazine is administered concomitantly."

2. The following phrase should be added to the second paragraph: "or those with a history of ulcer disease."

3. The following paragraphs should be added to this section:

"Promethazine can block and even reverse some of the actions of epinephrine."

"Promethazine should be used cautiously in persons with acute or chronic respiratory impairment, particularly children. The cough reflex may be suppressed. Drying effects may result in inspisation of secretions in lower respiratory disease."

F. ADVERSE REACTIONS:

1. Prior to the paragraph entitled "CNS Effects," the following statements should appear: "Pharmacological similarities among the phenothiazine derivatives requires consideration when promethazine is administered. There have been occasional reports of sudden death in patients receiving phenothiazine derivatives chronically."

2. The paragraph entitled "Cardiovascular Effects" should be revised. This paragraph should be rewritten as follows: "Postural hypotension is the most common cardiovascular effect of promethazine. Reflex tachycardia associated with mild increases in blood pressure have been seen with the use of promethazine hydrochloride. Bradycardia, faintness, dizziness and EKG changes, including blunting of T waves and prolongation of the Q-T INTERVAL may be seen. INTERARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY."

3. The paragraph entitled "Gastrointestinal" should be modified to read: "Anorexia, nausea, vomiting, epigastric distress, constipation, diarrhea and dry mouth have been reported."

4. Insert the following paragraph: "Genitourinary: Urinary frequency, dysurea and urinary retention may occur."

5. In the paragraph entitled "Allergic Reactions," delete the phrase, "at the injection site" so that the sentence will now read: "These include urticaria, dermatitis, asthma, and photosensitivity." The second sentence should read as follows: "Edematous reactions, such as laryngeal edema, angiodema and anaphylactoid reactions may occur."

6. The section entitled "Paradoxical Reaction" should be modified to read as follows: "Hyperexcitability and abnormal movements have been reported in children as manifestations of central nervous system toxicity following a single dose of 25 to 50 mg of promethazine hydrochloride. Nightmares and psychotic behavior have also been reported. Improper management of the central nervous system toxicity may result in respiratory and central nervous system depression."

7. Following the ADVERSE REACTIONS section, insert another section which is to be entitled "DRUG INTERACTIONS: MAO INHIBITORS AND THIAZIDE DIURETICS PROLONG AND INTEN-

SIFY THE ANTICHOLINERGIC EFFECTS OF PROMETHAZINE. Combined use of MAO inhibitors and promethazine may result in hypertension and extrapyramidal reactions."

"Narcotics—the CNS depressant and analgesic effects of narcotics are potentiated by phenothiazines (See WARNINGS)."

"The following drugs may result in potentiation of phenothiazine effects:

Oral Contraceptives
Progesterone
Reserpine
Nylidrin Hydrochloride"

G. DOSAGE AND ADMINISTRATION:

1. Under "DOSAGE AND ADMINISTRATION" following the first paragraph, insert the sentence, "When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg/ml at a rate not to exceed 25 mg per minute."

2. In the paragraph entitled "Sedation," insert the word "adult" between the words "hospitalized" and "patient" so that the paragraph will read as follows: "In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of promethazine hydrochloride."

3. In the paragraph entitled "Obstetrics," at the end of the paragraph insert the phrase "not to exceed 75 mg in any 8 hour period, or a total of 100 mg in any 24 hour period."

4. In the paragraph entitled "Children," add the following statement: "Promethazine should not be used for antiemetic effect in vomiting of unknown etiology in children (See WARNINGS)."

H. MANAGEMENT OF OVERDOSAGE:

In the second paragraph following the third sentence, insert this sentence, "Extrapyramidal symptoms may be treated with antiparkinson drugs such as barbiturates or diphenhydramine hydrochloride." The remainder of the paragraph is acceptable.

I. HOW SUPPLIED:

A HOW SUPPLIED section must be included in the package insert.

Please submit your revised labeling in draft form for our review.

Sincerely yours,

/s/

Margaret A. Clark, M.D.
Director
Division of Surgical-
Dental Drug Products
Bureau of Drugs

MINUTES OF ADVISORY COMMITTEE MEETING HELD OCTOBER 14, 1976 (DEFENDANT'S TRIAL EXHIBIT S)

FOOD AND DRUG ADMINISTRATION
BUREAU OF DRUGS
ANESTHESIOLOGY ADVISORY COMMITTEE
EIGHTEENTH MEETING

October 14, 1976

Teakwood Suite
The San Francisco Hilton
Mason and O'Farrell Streets
San Francisco, California

MEMBERS OF THE ADVISORY COMMITTEE PRESENT:

Betty J. Bamforth, M.D.—Chairman
Philip R. Bromage, M.B.
Burnell R. Brown, Jr., M.D., Ph. D.
Helmut F. Cascorbi, M.D., Ph. D.
Athole G. Jacobi, M.D.
Kenneth Sugioka, M.D.

MEMBERS OF THE ADVISORY COMMITTEE ABSENT:

M. Robert Knapp, M.D.

BUREAU OF DRUGS PERSONNEL IN ATTENDANCE:

Gerald M. Rachanow, Executive Secretary
Margaret A. Clark, M.D., HFD-160
Patricia H. Russell, M.D., HFD-160
David L. Scally, M.D., HFD-160

PUBLIC ATTENDEES:

Jeffrey M. Baden—Stanford, California
Harold H. Borgstodt, M.D.—Rochester, New York
Terrell A. Crowley, Ph.D.—North Chicago, Illinois
Edmond I. Eger, II, M.D.—San Francisco, California
Louis L. Ferstandig, Ph.D.—Hackensack, New Jersey

Ben Hitt, Ph.D.—Stanford, California
Duncan A. Holaday, M.D.—Miami, Florida
John B. Jewell, M.D.—New York, New York
Richard I. Mazze, M.D.—Stanford, California
James L. McMahon—New York, New York
William A. Mischel—Lexington, Massachusetts
W. D. Northcroft—San Mateo, California
James L. Ryan—Santa Ana, California
Charles W. Simons—Lexington, Massachusetts
Bradley E. Smith, M.D.—Nashville, Tennessee
Ross C. Terrell—New Providence, New Jersey
James F. Vitcha—Cape Coral, Florida

ANESTHESIOLOGY ADVISORY COMMITTEE

The meeting was called to order at 9:00 A.M., Dr. Betty J. Bamforth, Chairman, presiding. Dr. Athole G. Jacobi, the newest Committee member, was introduced.

OPEN PUBLIC HEARING:

An opportunity was provided for members of the public present to make comments or ask questions relevant to the Advisory Committee's agenda or other work, and no comments or questions were presented.

OPEN COMMITTEE DISCUSSION:

The first item on the agenda was a short presentation by the Executive Secretary concerning recent changes in FDA advisory committee procedures.

* * *

The second item on the agenda was the proposed package insert revision for Phenergan (promethazine hydrochloride) Injection, NDA 8-857, The FDA has proposed that the first paragraph of the CONTRAINDICATIONS section of the package insert be revised to state: "Promethazine is contraindicated in comatose states, in patients who have received large amounts of

central nervous system depressants (alcohol, barbiturates, narcotics, etc.), in patients who have bone marrow depression, and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine." The manufacturer, Wyeth Laboratories, disagrees with the contraindication to the use of Phenergan Injection in bone marrow depression. The question presented to the Advisory Committee was whether "Based on the limited case reports of blood dyscrasias which have been received, should the use of Phenergan Injection be contraindicated in bone marrow depression? or would a WARNING statement be more appropriate at this time?" The Committee agreed that present evidence does not warrant a contraindication, but that it certainly warrants a warning.

The FDA medical officer had suggested that since arterial injection is not an acceptable means of administering drugs that the second paragraph of the CONTRAINDICATIONS section (concerning intra-arterial injection) be deleted. Wyeth Laboratories has stated its strong feeling that this contraindication to the intra-arterial injection of Phenergan is entirely appropriate in its present location and is essential to ensure the safe use of this drug. The question presented to the Advisory Committee was "Should the reference to intra-arterial injection remain or be deleted from the CONTRAINDICATIONS section?" The Committee agreed that it had no objections to including this statement under CONTRAINDICATIONS and that, because of the seriousness of the problem, statements concerning intra arterial injection which appear in the WARNINGS section should remain there also.

One of the Committee members commented that the present statement (i.e., Subcutaneous injection is not recommended; ...) concerning subcutaneous injection

was pretty mild and that this statement should be made stronger or should appear in the CONTRAINDICATIONS section because there have been at least three or four cases of abscesses developing because of subcutaneous injection of the drug. He added that tissue necrosis and slough may follow subcutaneous injection and that the drug should be given by deep intra-muscular injection. The Committee agreed that an additional paragraph should be added to the CONTRAINDICATIONS section stating that Phenergan Injection should not be given by subcutaneous injection (because of the possibility of abscesses developing and of tissue necrosis) and that deep intra-muscular injection is the recommended route of administration of the drug.

The FDA medical officer had suggested that under the WARNINGS section of the package insert in the paragraph entitled Usage in Pregnancy that the following sentence be added: "Jaundice and hyperreflexia have been reported in infants whose mothers received phenothiazines during pregnancy." A number of literature references had been provided to Committee members and the question presented to the Committee was "Do you feel that sufficient evidence exists to require a statement about jaundice and hyperreflexia in infants of mothers receiving phenothiazines in labor?" The Committee and the FDA medical officer agreed that this statement could not be substantiated via the literature and should not be included in this section of the package insert.

Under the WARNINGS subsection entitled Use in the Elderly (approximately 60 years or older) the FDA has suggested the following statement be added as a second sentence "Because of reduced therapeutic requirements, dosage should be reduced accordingly." Wyeth Laboratories disagrees with a reduced therapeutic re-

quirement for Phenergan in elderly patients. The question presented to the Advisory Committee was "Do you agree with the statement that therapeutic requirements are, in general, decreased in elderly patients, and if so, that the Phenergan Injection package insert should contain such a statement?" The Committee agreed that a generic statement informing that "Since therapeutic requirements for sedative drugs tend to be lees in elderly patients, the dosage of Phenergan should be reduced for these patients." should be added to this section of the package insert.

The next question presented to the Advisory Committee was "Should information concerning the potentiation of toxicity of local anesthetics described in the article from Dental Abstracts (April 1975, pp. 238-239) be incorporated into the WARNINGS section of the package insert?" The Committee agreed that there does not currently appear to be any great difficulty associated with the combination of local anesthetics and promethazine, and that there is no reason for including any such warning in the package insert.

It was noted that Phenergan is frequently used in combination with narcotic and more potent anticholinergic agents such as scopolamine and atropine. The question presented to the Advisory Committee was "Would it be appropriate for the package insert to contain a statement (in the PRECAUTIONS section) cautioning against cough suppression and inspissation of secretions in lower respiratory tract disease?" The Committee agreed that this is too small a problem to put in the PRECAUTIONS section of the package insert.

The Committee was asked whether the following or a similar statement should appear in the ADVERSE REACTIONS section of the package insert: "Pharma-

cological similarities among the phenothiazine derivatives requires consideration when Phenergan is administered. There have been occasional reports of sudden death in patients receiving phenothiazine derivatives chronically." or would this type of statement be more appropriate under the "DRUG INTERACTIONS" section of the package insert? The Committee agreed that the statement as made does not imply a drug interaction and should not be included in this section of the package insert. The Committee agreed that a generic statement common to all phenothiazines should be included in the ADVERSE REACTIONS section, e.g., that sudden death has been reported following chronic therapy with these drugs.

The FDA has proposed that the subsection entitled "Paradoxical Reaction" be modified to read as follows: "Hyperexcitability and abnormal movements have been reported in children as manifestations of central nervous system toxicity following a single dose of 25 to 50 mg. of promethazine hydrochloride. Nightmares and psychotic behavior have also been reported. Improper management of the central nervous system toxicity may result in respiratory and central nervous system depression." The manufacturer has responded that the reference to central nervous system "toxicity" of promethazine is misleading and that the term "toxicity" is inappropriately used; also that the sentence referring to "improper management of the central nervous system toxicity is misleading and that it is not clear what information this sentence is trying to convey." The questions presented to the Committee were (1) Do you agree that paradoxical reactions are, in fact, evidence of CNS toxicity of promethazine and should be so identified to avert further dosing to "control" the reaction? and (2) Do the suggested sentences convey this infor-

mation? If not, how should this section be revised to convey this information? The FDA medical officer clarified the reasoning for proposing the word "toxicity," e.g., if you call it a toxic reaction, then the physician will not give more promethazine in an attempt to control the abnormal reaction which has occurred. The Committee agreed that the reaction need not be classified as a "toxicity" and that it is more important that the package insert state that the drug should be discontinued if such a reaction occurs. The Committee agreed that the following information should be stated in the package insert: "Hyperexcitability and abnormal movements which have been reported in children following a single administration of promethazine may be manifestations of relative overdosage, in which case consideration should be given to the discontinuation of the promethazine and to the use of other drugs." The Committee further stated that the name of the subsection should be changed from "Paradoxical Reaction" to "Overdosage."

Under DOSAGE AND ADMINISTRATION, the following question was presented to the Committee: "Based on knowledge that Phenergan crosses the placental barrier within 90 seconds and may reach 95% of maternal concentration in cord blood (Fisher, D. E. and J. B. Paton 'The Effect of Maternal Anesthetic and Analgesic Drugs on the Fetus and Newborn,' Clin. Obstet. Gynecol. 17, 275-287, June 1974), would suggested dosage limits of 75 mg. in any eight hour period and 100 mg. in 24 hours be appropriate in the OBSTETRICS subsection of the DOSAGE AND ADMINISTRATION section? (The manufacturer's recommended pediatric dosage is 0.5 mg./lb. or approximately 3.5 mg. for a seven lb. baby.)" The Committee agreed that 100 mg.

is a reasonable and sound recommendation for maximum obstetrical dosage during a 24-hour period.

The Committee was also asked: "Since it appears that it may be difficult to aspirate or be aware of intra-arterial pressure when using Wyeth's Tubex system to administer this drug and that more intra-arterial injections occur when the Tubex system is used is used in place of a plain needle and syringe, should the use of Tubex be discussed in this section (or perhaps in the PRECAUTIONS section)?" The Committee agreed that the following statement should be added under the Parenteral Administration subsection of the WARNINGS section: "If a Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set."

The following general question was presented to the Committee: "In view of the fact that a physician may prescribe any of the Phenergan dosage forms for premedication or sedation, would a single package insert for all Phenergan dosage forms (excluding the expectorant combinations) be appropriate? or would a separate package insert for the injection be more appropriate in view of the following statement which appears in the current package insert, e.g., 'The injectable form of promethazine hydrochloride is indicated for the following conditions when use of the oral form is impractical'?" Committee members felt that the CNS effects described in pediatric patients were more likely to occur in a clinical situation with the oral dosage form rather than the injectable form. The committee agreed that a single package insert for all Phenergan dosage forms (excluding the expectorant combinations) would be more appropriate than separate inserts.

One Committee member noted that there have been reports of deep vein thromboses due to intravenous injections made in the lower leg. Another Committee member mentioned that Phenergan should also not be injected into a small hand vein because of the limited blood circulation. The Committee agreed that a generic statement could be added to the package insert that deep vein thromboses occur more commonly when drugs are injected into the lower extremities. One Committee member suggested an editorial change, e.g., where the package insert uses the word agent(s), this should be changed to the word drug(s).

The third item on the agenda was a discussion of the comments received to the Federal Register proposed rule (41 FR 14883, April 8, 1976) regarding "Requirements for Inhalation Anesthetic Drug Products—Studies for Carcinogenic and Teratogenic Potential."

* * *

This concluded the open portion of the meeting.

CLOSED PRESENTATION OF DATA:

A new protocol for Phase 1 studies under IND 12,639 was discussed. Representatives of the sponsor of IND 11,551 and their clinical investigators were present to discuss the preclinical and Phase 1 studies of this drug.

CLOSED COMMITTEE DELIBERATIONS:

Specific questions were presented concerning the protocol for IND 12,639 and the studies conducted under IND 11,551, and a number of recommendations were made concerning the investigation of these drugs.

The next meeting was tentatively scheduled for March 1977.

The meeting adjourned at 2:45 P.M.

I certify that I attended the eighteenth meeting of the Anesthesiology Advisory Committee of the Food and Drug Administration on October 14, 1976, and that these minutes accurately reflect what transpired.

Chairman /s/
Betty J. Bamforth, M.D.

Executive Secretary /s/
Gerald M. Rachanow

LETTER FROM WYETH TO FDA DATED SEPTEMBER 21, 1981 (DEFENDANT'S TRIAL EXHIBIT T)

WYETH LABORATORIES INC. [logo] *Box 8299, Philadelphia, Pennsylvania, 19101*
(215) 688-4400

REGULATORY AFFAIRS

September 21, 1981

NDA 8-857

James P. Mann, M.D., Director
Division of Surgical-Dental Drug Products
Food and Drug Administration
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20857

Dear Doctor Mann:

Reference is made to our approved NDA No. 8-857 for "Phenergan®, promethazine hydrochloride, Injection" and to the Federal Register Notices of June 26, 1979 and May 16, 1980 relating to Format and Content of Physician Labeling.

We are pleased to provide herewith draft copy of the package inserts for this product revised to conform to the requirements contained in the Federal Register Notice of June 26, 1979.

Sincerely yours,

WYETH LABORATORIES INC.

Paul V. Uses

Manager, Drug Regulatory Affairs Section

PVU:reb
Encs.

bcc: Dr. Agersborg
Mr. Barry
Mr. Bathish
Mr. Golden
Dr. Gold
Dr. Lewis w/atts.
Mr. Ross
Dr. Shaw w/atts.
Mr. Spitznagel w/atts.

THIS BLOCK FOR PRODUCT [illegible]

WYETH LABORATORIES REQUEST FOR REVISED PRODUCT SPECIFICATION REFERENCE GEN MGMT STANDARD PROCEDURE [illegible]	SUBMIT SINGLE COPY TO DIRECTOR OF THE PROJECT COORDINATION DIV., [illegible]	[illegible]
PRODUCT NAME Phenergan® (promethazine HCl) Injection		PRODUCT AND/OR PACKAGE NO.
REQUEST TO CHANGE EXISTING SPECIFICATION FOR: ☐ FORMULA (NO CHANGE IN PRODUCT NO.) ☐ MANUFACTURING DIRECTIONS ☐ TESTING STANDARDS ☒ LABELING ☐ [illegible]		

DETAILED DESCRIPTION OF REQUEST (ATTACH MARKED-UP COPY OF CURRENT SPECIFICATION WHEN APPROPRIATE)
Attached.

REASON FOR REQUEST
The attached direction circular has been revised in accordance with FDA Guidelines published in the Federal Register for June 25, 1979, and in keeping with the schedule mandated in the Federal Register, Volume 45, No. 97, Friday, May 16, 1980. As stipulated in the latter publication, this draft labeling is to be submitted for FDA review and approval before being put into use; no labeling changes, therefore, are to be made at this time.

SUBMITTED BY		DATE SUBMITTED	[illegible]
/s/ Earl T. Lewis, M.D. /	/s/ Daniel L. Shaw, Jr., M.D.	9/18/81	3/1/82
APPROVAL TO BEGIN WORK ON [illegible]		DATE APPROVED	TARGET DATE FOR REVISED [illegible]

WYETH A.H.F.S. CATEGORY 4:00, 28:24, 56:20

PHENERGAN®

(promethazine HCL)

INJECTION

* * *

CONTRAINDICATIONS

Promethazine is contraindicated in comatose states, in patients who have received large amounts of central-nervous-system depressants (alcohol, barbiturates, narcotics, etc.) and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine.

Under no circumstances should promethazine be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see Warnings).

Phenergan injection should not be given by the subcutaneous route; evidence of chemical irritation has been noted and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

WARNINGS

Promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery. The concomitant use of alcohol or other central-nervous-system depressants may have an additive effect (see Precautions—"Drug Interactions"). Patients should be warned accordingly.

Inadvertent Intra-Arterial Injection

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injec-

tion of promethazine, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of this condition after it occurs, although sympathetic block and heparinization are commonly employed during the acute management because of the results of animal experiments with other known arteriolar irritants.

Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with promethazine. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

When used intravenously promethazine hydrochloride should be given in a concentration no greater than 25 mg. per ml. and at a rate not to exceed 25 mg. per minute. When administering any irritant drug intravenously it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended intravenous injection of promethazine, the injection should immediately be stopped to provide for evaluation of possible arterial placement or perivascular extravasation.

Injection into or near a nerve may result in permanent tissue damage.

Use in Children

Excessively large dosages of antihistamines, including promethazine, in children may cause hallucinations,

convulsions, and sudden death (see Adverse Reactions—"Paradoxical Reactions"). In children who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of injectable antihistamine CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN TO CHILDREN. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN CHILDREN, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN® ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN SHOULD BE AVOIDED IN CHILDREN WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME, OR OTHER HEPATIC DISEASES.

* * *

ADVERSE REACTIONS

CNS EFFECTS:

Drowsiness is the most prominent CNS effect of this drug. Extrapyramidal reactions may occur with high doses; this is almost always responsive to a reduction in dosage. Other reported reactions include dizziness, lassitude, tinnitus, euphoria, diplopia, nervousness, insomnia, tremors, convulsive seizures, oculogyric crises, excitation, catatonic-like states, and hysteria.

CARDIOVASCULAR EFFECTS:

Tachycardia, bradycardia, faintness, dizziness, and increases and decreases in blood pressure have been re-

ported following the use of promethazine hydrochloride injection. Venous thrombosis at the injection site has been reported. INTRA-ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see Warnings).

GASTROINTESTINAL:

Nausea and vomiting have been reported, usually in association with surgical procedures and combination drug therapy.

ALLERGIC REACTIONS:

These include urticaria, dermatitis, asthma, and photosensitivity. Occurrence of photosensitivity may be a contraindication to further treatment with promethazine or related drugs. Angioneurotic edema has been reported.

OTHER REPORTED REACTIONS:

Thrombocytopenic purpura and jaundice of the obstructive type have been associated with the use of promethazine. The jaundice is usually reversible on discontinuation of the drug. Subcutaneous injection has resulted in tissue necrosis. Nasal stuffiness may occur. Patients may occasionally complain of autonomic reactions such as dryness of the mouth and blurring of vision.

PARADOXICAL REACTIONS (OVERDOSAGE):

Hyperexcitability and abnormal movements which have been reported in children following a single administration of promethazine may be manifestations of relative over-dosage, in which case, consideration should be given to the discontinuation of the promethazine and to the use of other drugs. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

* * *

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use Phenergan if solution is discolored or contains a precipitate.

To avoid the possibility of physical and/or chemical incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

Important Notes on Administration

The preferred parenteral route of administration for promethazine hydrochloride is by deep intramuscular injection. The proper intravenous administration of this product is well-tolerated, but use of this route is not without some hazard.

INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see Warnings). SUBCUTANEOUS INJECTION IS CONTRAINDICATED AS IT MAY RESULT IN TISSUE NECROSIS (see Contraindications).

Injection into or near a nerve may result in permanent tissue damage.

When used intravenously, promethazine hydrochloride should be given in concentration no greater than 25 mg/ml at a rate not to exceed 25 mg. per minute; it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

ALLERGIC CONDITIONS:

The average adult dose is 25 mg. This dose may be repeated within two hours if necessary, but continued therapy, if indicated, should be via the oral route as soon as existing circumstances permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The average adult dose for amelioration of allergic reactions to blood or plasma is 25 mg.

SEDATION:

In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg. of promethazine hydrochloride.

PRE- AND POST-OPERATIVE USE:

As an adjunct to pre- or post-operative medication, 25 to 50 mg. of promethazine hydrochloride in adults may be combined with appropriately reduced doses of analgesics and atropine-like drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

NAUSEA AND VOMITING:

For control of nausea and vomiting the usual adult dose is 12.5 to 25 mg. not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or intravenously and dosage of analgesics and barbiturates reduced accordingly.

OBSTETRICS:

Phenergan in doses of 50 mg. will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25 to 75 mg. (average dose, 50 mg.) promethazine hydrochloride may be given

intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. Amnesic agents may be administered as necessary. If necessary, Phenergan with a reduced dose of analgesic may be repeated once or twice at four-hour intervals in the course of a normal labor. A maximum total dose of 100 mg. of Phenergan may be administered during a 24-hour period to patients in labor.

CHILDREN:

In children under the age of 12 years the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication the suggested dose is 0.5 mg. per pound of body weight in combination with an equal dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in children.

* * *

INTERNAL WYETH MEMORANDUM DATED MARCH 19, 1987 (PLAINTIFF'S SUMMARY JUDGMENT EXHIBIT 9)

[handwritten "File"]

INTERNAL CORRESPONDENCE

[logo]

to Dr. Earl Lewis	from James J. O'Shaughnessy
company WLI located Radnor A-2	company WLI located Radnor C-2
subject Phenergan® Injection Labeling Content and Format Evaluation by the FDA	date March 19, 1967

Dear Earl:

During a recent telephone conversation with Dr. David L. Scally of the FDA's Division of Surgical-Dental Drug Products, I learned that his Division plans to send a letter to Wyeth requesting extensive revisions in the text of the package insert for Phenergan Injection.

The letter from the FDA will address two supplemental applications filed with the Surgical-Dental Division—S-009, filed September 21, 1981 (draft copy) and S-012, filed November 13, 1986 (final printed labeling). Attached please find copies of the Wyeth letters covering both of the aforementioned submissions.

A proposed copy of the correspondence to be sent to Wyeth is currently being circulated within the Surgical-Dental Division, and the letter will be issued as

soon as all pertinent staff members provide their concurrence.

Dr. Scally agreed to provide the attached draft of his evaluation or our submissions, and the corresponding follow-up letter to be distributed to Wyeth. He does not expect the final versions of either document to vary significantly from his proposed copies. He indicated that the preeminent editorial change recommended in his communications is the incorporation of labeling relative to the recognition and management of unintended intraarterial injection.

The final letter from the FDA will solicit a response from Wyeth within 90 days. So, unless you have any objections to the recommendations provided by Dr. Scally, please make the necessary preliminary arrangements to provide for the revisions. I shall send you FDA's official correspondence as soon as it arrives.

Sincerely,

/s/

James J. O'Shaughnessy

JJO:dlo
25129

cc: Dr. Agersborg
Mr. Bathish
Dr. Canavan
Dr. Deith
Mr. Golden
Mrs. Ivester
Mr. Krieg
Dr. Richards
Dr. Rogers
Mr. Ross
Mr. Spitznagel
Dr. Walker
Regulatory Routing

LETTER FROM FDA TO WYETH DATED MARCH 26, 1987 (PLAINTIFF'S TRIAL EXHIBIT 47)

[logo]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

Stamp: MAR 26, 1987

NDA 8-857/S-009

Wyeth Laboratories
P.O. Box 8299
Philadelphia, PA 19101

Attention: Paul V. Uses
Associate Director
Drug Regulatory Affairs

Gentlemen:

Please refer to your supplemental new drug application dated September 21, 1981 (S-009) submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Phenergan (promethazine HCl) Injection.

The supplemental application provides for revised labeling in conformance with the Labeling Format Revision Program (21 CFR 201.56 and 201.57).

Reference is also made to the agency letter dated November 5, 1984, requesting further revisions in the labeling. We have not yet received a response to the referenced letter. The following comments, most of which

were conveyed to you by Dr. D. Scally, should be incorporated in the revised labeling. Please note that the comments include some deficiencies which were noted in S-012 dated November 13, 1986, as well as those noted in the original labeling supplement dated September 21, 1981.

The labeling should be revised as follows:

DESCRIPTION

The DESCRIPTION section of the package insert should add the pH of the drug product as well as the molecular formula and weight of the drug substance.

CLINICAL PHARMACOLOGY

It is suggested that the first paragraph of this section be rephrased as follows:

> "Promethazine is a phenothiazine derivative, which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopaminergic (CNS) action.
>
> "Promethazine is an H_1 receptor blocking agent. In addition to its antihistamine properties, it provides clinically useful sedative and antiemetic effects. In therapeutic dosages, promethazine produces no significant effects on the cardiovascular system."

CONTRAINDICATIONS

Please add the following statement to the CONTRAINDICATIONS section:

1. Conclude the first paragraph with: "... (hypersensitivity to promethazine) ... or other phenothiazines."

WARNINGS

Please revise your WARNINGS discussion of Inadvertent Intra-arterial Injection according to the following text:

"INADVERTENT INTRA-ARTERIAL INJECTION: There are reports of necrosis leading to gangrene, requiring amputation, following injection of promethazine, usually in conjunction with other drugs; the intravenous route was intended in these cases, but arterial or partial arterial placement of the needle is now suspect. The mechanism is uncertain, however, animal experiments with other arteriolar irritants suggest that the initiating factor may be platelet aggregation and thrombosis starting distal to the site of injection.

"The first sign may be the patient's reaction to a sensation of fiery burning, roughly following the distribution path of the injected artery; no more drug should be injected until the situation is remedied. Blanching may be present early, may be transient or may not be noted at all. Blotchy cyanosis and dark discoloration usually follows.

"There is no established treatment other than prevention:

1. Beware of the close proximity of arteries and veins at commonly used injection sites and consider the possibility of aberrant arteries.

2. When used intravenously, promethazine hydrochloride should be given in a concen-

tration no greater than 25 mg/ml and at a rate not to exceed 25 mg/minute. Injection through a properly running intravenous infusion may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant.

3. Subcutaneous swelling near the site of injection calls for discontinuation of promethazine administration and reevaluation of the situation. This sign may be indicative of venous extravasation, which may result in localized necrosis, or it may signify partial arterial placement of the needle or catheter.

4. Beware that the characteristic bright-red color of arterial blood is discolored by contact with promethazine. (Italics or different print underlined.)

"Post injury injection of vasodilators an/or arterial infusion of parenteral fluids are generally regarded as being of no value in altering outcome. Animal experiments and published individual case reports concerned with a variety of arteriolar irritants suggest that one or more of the following may be of benefit in reducing the area of necrosis:

1. Arterial injection of heparin at the site of injury, followed by systemic anticoagulation.

2. Sympathetic blood (or brachial plexus block in the arm), if anticoagulant therapy permits.

3. Intra-arterial glucocorticoid injection at the site of injury, followed by systemic steroids.

4. A recent case report (non-promethazine drug injury) suggests that intra-arterial urokinase may promote fibrinolysis, even if administered late in treatment."

The references supporting the above discussion are:

1. G.S.Buckspan, et.al., Intraarterial Drug Injury: Studies of Etiology and Potential Treatment, JL. SURG. RES. 24(4): 294-301, 1978.

2. M.P.Wiedeman, et. al., In Vivo Microscopic Observations of Intra-Arterial Injections of Barbiturates, JL. SURG. RES. 22(2): 94-108, 1977.

3. S.S.Brown, et. al., Intra-Arterial Barbiturates, BRIT. JL. ANAES. 40: 13-19, 1968.

4. J.S.Mathers & B. Goodhead, Intra-arterial Methohexitone and Thiopentone, ANAESTHESIA 21(1): 81-85, 1966.

5. G.A.Webb & N.Lampert, Accidental Arterial Injections, AM. J. OBST. & GYNEC. 101(3): 365-371, 1 June 1968.

6. H.S.Engler, et. al., Production of Gangrenous Extremities by Intra-Arterial Injections, AMERICAN SURGEON 30(9): 602-607, Sept. 1964.

7. D.L.Hager & J.N.Wilson, Gangrene of the Hand Following Intra-Arterial Injection, ARCH. SURG. 94: 86-89, Jan. 1967.

8. R.F.Lynas & W.I.K.Bisset, Intra-Arterial Thiopentone, ANAESTHESIA 24(2): 257-261, April 1969.

9. G.Corser, et. al., Ischaemia Following Self Administered Intra-Arterial Injection of Methylphenidate and Diamorphine, ANAESTHESIA 40: 51-54, 1985.

10. D.J.Waters, Intra-Arterial Thiopentone, ANAESTHESIA 21(3): 346-356, July 1966.

11. Correspondence Regarding Thiopental and Thiamylal (3 Letters): 1. L.C.Mark, 2. J.W.Dundee, 3. S.Dohi & H.Naito. ANESTHESIOLOGY 59: 153-155, 1983.

12. D.Albo, K.Reemtsma, et. al., Effect of Intra-Arterial Injections of Barbiturates, AMERICAN JL. OF SURGERY 120: 676-678, November 1970.

13. E.C.Klatte, et. al., Toxicity of Intra-Arterial Barbiturates and Tranquilizing Drugs, RADIOLOGY 92(4): 700-704, March 1969.

14. M.L.Nahrwold, et. al., Inadvertent Intra-Arterial Injection of Mephenteramine, ROCKY MOUNTAIN MEDICAL JOURNAL, 70(9): 38-39, September 1973.

15. G.Enloe, et. al., Hazards of Intra-Arterial Injection of Hydroxyzine, CANADIAN ANAES. SOC. JL. 16(5): 425-428, September 1969.

16. H.S.Engler, et. al., Gangrenous Extremities Resulting from Intra-Arterial Injections, ARCH. SURG. 94: 644-651, May 1967.

17. J.B.Kinmonth & R.C.Shepherd, Accidental Injection of Thiopentone Into Arteries, Studies of

Pathology and Treatment, BRITISH MEDICAL JOURNAL, 2: 914-918, 1959.

18. D.Goldsmith & N.Trieger, Accidental Intra-Arterial Injection: A Medical Emergency, ANESTHESIA PROGRESS 22(6): 180-183, Nov.-Dec. 1975.

19. R.Miller, et. al., Intra-Arterial Injection of a Barbiturate—A Case Report, ANESTHESIA PROGRESS 23(1): 25-27, Jan.-Feb. 1976.

20. H.H.Stone & C.C.Donnelly, REVIEW ARTICLE, The Accidental Intra-Arterial Injection of Thiopental, ANESTHESIOLOGY 22: 995-1006, 1961.

Please add the following statements to the WARNINGS section:

"Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or in combination with narcotics or local anesthetics which may also affect seizure threshold.

Promethazine has been associated with crib death and should be avoided in patients with a history of sleep apnea.

"Anticholinergic properties of promethazine have resulted in precipitation of acute narrow angle glaucoma, pyloroduodenal obstruction and urinary tract obstruction. Consideration should be given to the risk of these in prescribing promethazine for patients with a known predisposition to these complications such as those with stenosing peptic ulcer or benign prostatic hypertrophy.

"Administration of promethazine has been associated with reported cholestatic jaundice. This should be taken into consideration when interpreting laboratory results and when selecting medication in patients with impaired liver function.

"There are no data on safety or efficacy of use of promethazine injection to treat an acute asthmatic attack, therefore, such use is not recommended."

PRECAUTIONS

General

Please delete the first paragraph as this is now covered elsewhere ("Drugs having anticholinergic ... obstruction.")

Information for Patients

Please add the following paragraphs to this subsection:

"When appropriate, patients should be instructed to report any involuntary muscle movements or unusual sensitivity to light to their physician.

"When appropriate, it should be recommended that children be supervised to avoid potential harm in bike riding or other activities while their ability to react to hazardous situations is impaired.

Carcinogensis, Mutagensis, Impairment of Fertility

Revised labeling for carcinogensis, mutagensis, impairment of fertility and pregnancy is not supported by documented studies of promethazine concerning the Ames mutagensis study and rat teratology feeding study at doses of 6.25 and 12.5 mg/kg. These studies should be submitted to support the proposed labeling.

Pregnancy, Teratogenic Effects

As stated in your February 29, 1984, the statement "Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters," should be included.

Labor and Delivery

The discussion of Labor and Delivery (subsection of PRECAUTIONS) adds information to the effect that the drug is not apt to produce excessive sedation to mother or fetus when it is given as recommended, that the drug does not appreciably effect the duration of labor or delivery or the need for intervention or resuscitation in the process of delivery, and that there is no evidence that the drug if used during labor and delivery will have an effect on later growth, etc. No documentation is offered for any of these new claims.

The drug is approved for use in obstetrics, and this approval is not a subject of inquiry at this time. What is being questioned is the addition of unusual claims as to lack of side effects without submission of the data for review. These claims cannot he added to the prescription drug labeling until:

1. Satisfactory summaries, based upon adequate and well controlled studies, are submitted for review.
2. These studies are reviewed by our staff and you receive an "approvable" letter requesting the submission of final printed labeling.

In the event that these claims cannot be documented as specified above, this subsection of the

labeling shall state that the information is unknown (see 201.57(f)(7), page 37465 of the Federal Register Notice dated June 26, 1979).

Please also add to the following to the discussion of Labor and Delivery:

> "Promethazine administered during labor and delivery inhibits platelet aggregation (see nonteratogenic effects)."

OVERDOSAGE

The discussion of treatment of hypotension should begin by recommending that the treatment of choice is administration of intravenous fluids, accompanied by repositioning if indicated. The second sentence ("Severe hypotension—or phenylephrine") should be modified to read: "In the event that vasopressors are considered for the management of severe hypotension or hypotension which does not respond to intravenous fluids, etc., the administration of levarterenol or phenylephrine should be considered." Continue on with the third sentence and the rest of this section as contained in the September 21, 1981 submission.

DOSAGE & ADMINISTRATION

Please delete the sentence, under OBSTETRICS which reads: "Amnesic agents may be administered as necessary." There is no reason to single out this particular type of combined drug usage unless there is either substantial supporting data or significant drug interaction information. Perhaps this is a holdover from a previous era when amnesic agents were more popular with obstetricians.

HOW SUPPLIED

The following items should be included:

The HOW SUPPLIED section should also contain the storage temperature (range) based on stability data of the drug product. Although not mandatory, if an NDC number is added, it should be complete (e.g., NDC 0008-9142-01, lot#1860317, Tubex® Fast Trak® Syringe, 1 syringe of 2 ml size).

The text for the Direction for use should be identical. Please compare and contrast the final printed package insert number C13727-1 with C1 3477-1 issued March 29, 1985. The former is acceptable if the latter will be phased out.

Please submit revised draft labeling as soon as possible.

Sincerely yours,

/s/

Patricia H. Russell, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and
Review
Center for Drugs and Biologics

Stamp: RECEIVED
MAR 31 1987
DRUG REGULATORY AFFAIRS

INTERNAL WYETH MEMORANDUM DATED DECEMBER 1, 1987 (PLAINTIFF'S TRIAL EXHIBIT 46)

INTERNAL CORRESPONDENCE

[logo]

[handwriting: PVU
Pls. handle
[illegible 12/3]]

[illegible stamps and handwriting]

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to List Below	from Earl T. Lewis, M.D. (initials)
company W-A located Radnor	company W-AR located Radnor
subject Labeling Changes for Phenergan® Injection Direction Circular	date December 1, 1987

Mr. Bathish
Dr. Deitch
Mr. Meaney
Dr. Walker
Mr. Ross

Attached is a proposed revision to the Phenergan Injection direction circular which deals specifically with the section on "INADVERTENT INTRAARTERIAL INJECTION" and is contained in the "WARNINGS" section. A change in this section has been requested by the FDA in several letters we have received this year

beginning with Dr. Russell's letter of March 26, 1987 to Mr. Paul Uses.

Also attached for your perusal and comparison are copies of the specific wording proposed by FDA as well as the section on Inadvertent Intraarterial Injection that is contained in our current Phenergan Injection direction circular.

Please review this proposed revision and make any comments or suggested changes on your copy and return it to me by Friday, December 11, 1987 so that final copy can be provided to the FDA within the time limits imposed.

Thank you for your assistance.

When preparing to give promethazine intravenously, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. There are reports of severe tissue injury, including necrosis with resultant gangrene requiring amputation, following the injection of promethazine, usually in conjunction with other drugs meant for intravenous use. Although the intravenous route was intended in all these cases arterial or partial arterial placement of the needle is now suspect. The mechanism of producing this injury is uncertain, however animal experiments with other arteriolar irritants suggest that the primary cause may be platelet aggregation and thrombosis starting distal to the site of injection.

The first indication of this problem is usually the patient's complaint of severe pain or sensation of fiery burning, roughly following the distribution path of the injected artery. At the first complaint of any pain during the intended intravenous injection of promethazine,

the injection should be stopped immediately and evaluated for possible arterial placement of the needle. Blanching may be present early, may be transient or may not be noted at all. Blotchy cyanosis and dark discoloration usually follow. Pain is usually persistent and the skin temperature distal to the injection site may be decreased.

There is no established treatment that has been shown to be successful in the management of this condition after it occurs. Post injury injection of vasodilators and/or arterial infusion of parenteral fluids are generally regarded as being of no value in altering outcome. Animal experiments and published individual case reports concerned with a variety of arteriolar irritants suggest that one or more of the following may be of benefit in reducing the area of necrosis:

1. Heparinization with continuous intra-arterial injection of heparin proximal to the site of injury until pain and swelling have subsided (up to two weeks).

2. Sympathetic block (or brachial plexus block in the arm), if anticoagulant therapy permits.

3. Intra-arterial glucocorticoid injection at the site of injury, followed by systemic steroids.

4. A recent case report (non-promethazine drug injury) suggests that intra-arterial urokinase may promote fibrinolysis, even if administered late in treatment.

Since prevention is the only method shown to be effective in dealing with this problem, the following points are among those that should be considered in its prophylaxis:

1. Beware of the close proximity of arteries and veins at commonly used injection sites and consider the possibility of aberrant arteries.

2. When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg/ml and at rate not to exceed 25 mg/minute. Injection into an intravenous infusion set that is known to be running properly should decrease the possibility of inadvertently injecting promethazine intra-arterially. In addition, this results in delivery of a lower concentration of any arteriolar irritant.

3. Subcutaneous swelling near the site of injection calls for discontinuation of promethazine administration and reevaluation of the situation. This sign may be indicative of venous extravasation, which may result in localized necrosis, or it may signify partial arterial placement of the needle or catheter.

4. Be aware that the characteristic bright-red color of arterial blood is discolored by contact with promethazine (italics or different print underlined) so that the aspiration of dark blood does not preclude intra-arterial needle placement.

* * *

BEST AVAILABLE COPY

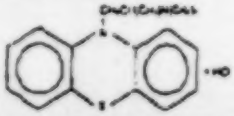
CI 2750-1 82.07

Wyeth®
Phenergan®
(promethazine HCl)
Injection

AHFS Category 4:00 28:24 56:20

Description

Phenergan HCl (10H-phenothiazine-10-ethanamine, N,N,α-trimethyl-, monohydrochloride) has the following structural formula:



Each mL of clear solutions under 25 mg or 50 mg promethazine hydrochloride with 0.1 mg sodium bisulfite, 0.91 mg calcium chloride, not more than 0.25 mg sodium metabisulfite and 5 mg phenol with sodium hydroxide/hydrochloric acid buffer.

Actions

Promethazine hydrochloride, a phenothiazine derivative, possesses both antihistaminic (blocking) and sedative properties. It is a competitive type of antihistamine which has been shown effective in the treatment of allergic conditions sensitive to such therapy, including the immediate hypersensitivity reactions to blood or plasma, various manifestations of the common cold, pruritic skin eruptions, and amelioration of reactions to insect bites and stings. Promethazine also has an antiemetic effect and is effective in the prevention and control of nausea and vomiting associated with surgical and obstetrical procedures. It potentiates the action of analgesics, thereby permitting reduction in dosage of these agents. Promethazine also has an anticholinergic effect and is a useful component of preanesthetic medication. It potentiates the action of barbiturates, narcotics, and other central nervous system depressants. Promethazine has a sedative effect in most patients, even in the presence of pain. Promethazine has an antitussive effect.

Indications

The injectable form of promethazine hydrochloride is indicated in the following conditions:

1. Prevention of allergic reactions to blood or plasma.
2. In preference to, or in addition to, epinephrine and other therapeutic measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
4. Active treatment of motion sickness.
5. Preoperative, postoperative, and obstetric (during labor) sedation.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
8. For sedation and relief of apprehension and tension produced when used in small doses before operative procedures.
9. Intravenously, in special surgical situations, such as repeated anesthetic sessions during surgery and post-operative pain control, with reduced amounts of meperidine or other narcotic drug (prior to its second or subsequent administration).

Contraindications

Promethazine is contraindicated in premature infants, in patients who have received large amounts of central nervous system depressants (narcotic analgesics, antihistamines including barbiturates, general anesthetics, tranquilizers, sedatives, nonbarbiturate hypnotics, etc.) and in children who have demonstrated an idiosyncrasy or hypersensitivity to promethazine.

Lower-to-normal dosages should be given by the subcutaneous route, especially if intravenous use has been noted, and medical history does indicate an increased susceptibility to subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection. The preferred parenteral route of administration is by deep intramuscular injection. The preferred parenteral route of administration is by deep intramuscular injection.

Warnings

Phenergan injection (drug) is [illegible] sodium metabisulfite, a sulfite that may cause allergic type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Promethazine may obscure the normal and/or physical signs required by the presence of pharmacologic incompatible liquids, such as drawing a vehicle or opening injection ampules. The administration use of sterile sodium hydroxide (including bacteriostatic sodium hydroxide, normal saline, sterile water, etc.) [illegible] may have an additive sedative effect. Patients should be advised accordingly.

USAGE IN PREGNANCY

The safe use of promethazine has not been established with regard to the possible adverse effects upon fetal development. The potential hazard for the use of this drug during pregnancy should be weighed against the possible benefit to the mother before giving this.

USE IN CHILDREN

Excessively large dosages of phenothiazines, including promethazine, in children may cause hyperpyrexia, convulsions, and sudden death. In children who are acutely ill, especially with dehydration, there is an increased susceptibility to dystonias with the use of promethazine hydrochloride injection.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN TO CHILDREN. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN CHILDREN, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, I.E., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN SHOULD BE AVOIDED IN CHILDREN IN WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME, OR OTHER HEPATIC DISEASES.

USE IN THE ELDERLY (APPROXIMATELY 60 YEARS OR OLDER)

Since the sedative requirements for sustaining drugs tend to be less in elderly patients, the dosage of Phenergan should be reduced or given [illegible].

OTHER CONSIDERATIONS

Drugs having anticholinergic properties should be used with caution in patients with asthmatic attack, narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder neck obstruction.

Phenergan should be used with caution in patients with bone marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known toxic agents.

INADVERTENT INTRAARTERIAL INJECTION

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular or intra-arterial injection of medication. Reports, sometimes with objective evidence of necrosis of [illegible] following intra-arterial injection of promethazine, usually in combination with other drugs irritating to arteries, have suggested that such severe effects may result from [illegible] and include gangrene requiring amputation. Such severe effects may result from [illegible] and include gangrene requiring amputation. Such severe effects may result from [illegible] and include gangrene requiring amputation.

Precautions

Promethazine may significantly affect the actions of other drugs. It may increase, prolong, or intensify the sedative action of central nervous system depressants, such as alcohol, sedatives (including barbiturates), tranquilizers, hypnotics, narcotics, narcotic analgesics, meperidine, etc. When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine may lead to restlessness and motor hyperactivity, in the absence of pain. These symptoms usually disappear with adequate control of the pain. Promethazine should be used cautiously in persons with cardiovascular disease or impairment of liver function.

Although neither of the recommended routes of administration has ever been reported with promethazine, the possibility should be considered in case of [illegible].

Adverse Reactions

CNS EFFECTS

Drowsiness is the most common CNS effect of promethazine. Confusion, [illegible] may occur with high doses. This is almost always responsive to reduction of dosage. Other reported reactions include [illegible], [illegible], [illegible],

LETTER FROM WYETH TO FDA DATED MAY 3, 1988 (DEFENDANT'S TRIAL EXHIBIT M)

RECEIPT COPY

WYETH-AYERST [logo] *LABORATORIES*

P.O. BOX 8299, PHILADELPHIA, PA 19101-1245 • *(215) 688-4400*

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

Stamp: REC'D [Illegible]

May 3, 1988

NDA No. 8-857/S-009

Philip G. Walters, M.D., Acting Director
Division of Surgical-Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Walters:

Reference is made to our approved new drug application no. 8-857 for "Phenergan®, promethazine hydrochloride, Injection" as well as to our September 21, 1981 (S-009) supplemental application, and subsequent amendments, providing package inserts revised to conform to the Federal Register notices relative to content and format labeling requirements for this product.

Reference is also made to your communications of May 26, 1987 and November 13, 1987 which requested additional changes in the text of the labeling covered by this supplemental application.

In response to your letters, we are pleased to provide herewith four draft copies of the revised Phenergan Injection package insert incorporating the changes recommended in your correspondence. Also, we have included additional medically significant information to the proposed text.

We trust that you will find this proposed labeling satisfactory and will so advise us at your earliest convenience.

Sincerely,

WYETH-AYERST LABORATORIES

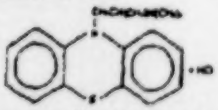
/s/

Paul V. Uses
Associate Director
Drug Regulatory Affairs

PVU:dlo
25352(4)

Wyeth®
Phenergan®
(promethazine HCl)
Injection

[redacted]



[redacted]

INSERT HERE:
Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S \cdot HCl$ and its molecular weight is 320.88. The pH for the drug product is between 4.0 and 5.5.

[redacted]

Clinical Pharmacology

DELETE THIS PARAGRAPH. SUBSTITUTE THE FOLLOWING:

Promethazine is a phenothiazine derivative, which differs structurally from the antipsychotic phenothiazines by the presence of a branched alkyl chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopaminergic (DA1) action.

Promethazine is an H1 receptor blocking agent. In addition to its antihistaminic properties, it exerted clinically useful sedative and antiemetic effects. In therapeutic dosages, promethazine produces no significant effects on the cardiovascular system.

Clinical effects are apparent within 15 to 20 minutes after intramuscular injection and within 3 to 5 minutes after intravenous injection; the duration of action is usually four to six hours, although effects may persist as long as 12 hours. Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demethylpromethazine are the predominant metabolites appearing in the urine.

[redacted]

and Usage

[redacted]

NDA-00005582

327

END PARAGRAPH WITH:
promethazine or other phenothiazines. .

ADD THE FOLLOWING WARNINGS:

Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or in combination with narcotics or local anesthetics which may also affect seizure threshold.

The anticholinergic properties of promethazine have resulted in precipitation of acute narrow angle glaucoma, pyloroduodenal obstruction and urinary tract obstruction. Although such conditions have been rare with promethazine, consideration should be given to the risk of these in prescribing promethazine, especially for patients with a known predisposition to these complications such as those with stenosing peptic ulcer or benign prostatic hypertrophy.

"There are no data on safety or efficacy of use of promethazine injection to treat an acute asthmatic attack, therefore, such use is not recommended."

"Administration of promethazine has been associated with reported cholestatic jaundice. This should be taken into consideration when interpreting laboratory results and when selecting medication in patients with impaired liver function.

DELETE THESE TWO PARAGRAPHS AND SUBSTITUTE THE INFORMATION FOUND ON THE NEXT PAGE

[redacted]

"se with caution in patients with lower respiratory disease, including asthma.

[redacted]

DELETE THESE FIVE LINES AND SUBSTITUTE THE INFORMATION FOUND DIRECTLY BELOW THEM

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.1 to 4.2

[redacted]

While antihistamines, including promethazine at a daily dosage level of 25 mg/kg intraperitoneally, have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man.

[redacted] with respect to the possible adverse effect on fetal development. Therefore,

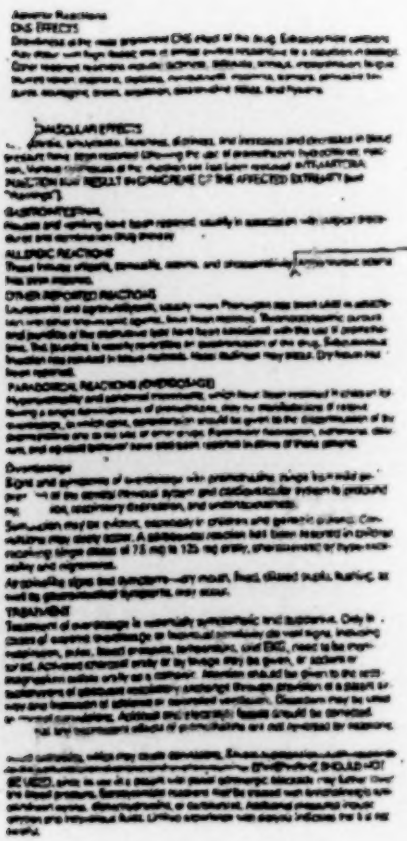
Promethazine administered during labor and delivery may inhibit platelet aggregation in the newborn. The clinical significance of this effect is unknown.

[redacted]

Limited data suggest that the use of Phenergan as a sedative during labor and delivery does not have an appreciable effect on the duration of labor or delivery or in increasing the chances that the newborn will require any type of intervention in the process of delivery when given as recommended. The effect on the later growth, development or functional maturation of the newborn when Phenergan has been used during labor and delivery is unknown.

[redacted]

[redacted]



INSERT HERE:
Occurrence of photosensitivity may be a contraindication to further treatment with promethazine or related drugs.

REPLACE THE SECOND SENTENCE WITH THE FOLLOWING:
The treatment of choice for resulting hypotension is administration of intravenous fluids, accompanied by repositioning if indicated. In the event that vasopressors are considered for the management of severe hypotension which does not respond to intravenous fluids and repositioning, the administration of levarterenol or phenylephrine should be considered.

[redacted] AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use Phenergan [redacted] if solution is discolored or contains a precipitate.

To avoid the possibility of physical and/or chemical incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

Injection

Treatment Dosage and Administration

The preferred parenteral route of administration for promethazine hydrochloride is by deep intramuscular injection. The deep intramuscular administration of the product is well-established but use of this route is not without some hazard.

[redacted] INTRAARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see "Warnings"). SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (see "Contraindications").

[redacted] ...within date or dose ... there may result in permanent tissue damage.

When used intravenously, promethazine hydrochloride should be given in concentrations no greater than 25 mg/mL, at a rate not to exceed 25 mg per minute (i.e. preferably by slowly passing the tubing of an intravenous infusion set that is known to be functioning satisfactorily).

ALL EMETIC CONDITIONS

The average adult dose is 25 mg. The dose may be repeated within two hours if necessary, but continued therapy, if indicated, should be with the oral route as soon as vomiting circumstances have ceased. After initiation of treatment, dosage should be adjusted to the smallest amount effective in relieving symptoms. The average adult dose for amelioration of emetic reactions in cases of pregnancy is 25 mg.

SEDATION

In management of adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of promethazine hydrochloride.

PRE- AND POSTOPERATIVE USE

As an adjunct to 50% of barbiturate medication, 25 to 50 mg of promethazine hydrochloride in adults may be sufficient with somewhat reduced doses of concomitantly administered analgesic drugs as required. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

NAUSEA AND VOMITING

For control of nausea and vomiting, the usual adult dose is 12.5 to 25 mg, not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or slowly intravenously, and barbiturates reduced accordingly.

[redacted]

Promethazine in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is sufficiently established, 25 to 75 mg (according to dose) of an analgesic/narcotic may be given intramuscularly or intravenously in combination with an agent of the phenothiazine class, such as promethazine hydrochloride, in reduced dosage. Administration of an analgesic/narcotic subsequently may be given in reduced dosage. Administration of an analgesic may be repeated once or twice at four-hour intervals in the absence of a specific labor pattern. A maximum total dose of 100 mg of Phenergan may be administered during a 24-hour period to patients in labor.

CHILDREN

In children under the age of 2 years, the dosage should not exceed half dose of the suggested adult dose. As an aid in arriving at the correct dose, the suggested dose of 0.5 mg per lb. of body weight of a child may be used. Administration of barbiturates and the appropriate dose of an antiemetic drug. Antiemetics should not be used in vomiting of unknown etiology in children.

DELETE THIS SENTENCE

ADD THE FOLLOWING SENTENCE AS THE FIRST PARAGRAPH UNDER THE SUBCATEGORY "CHILDREN":

Phenergan Injection should not be used in children less than 2 years of age.

(See Warnings).

How Supplied

[redacted] a products investigated as follows:

NDC 0008-0063-01, 25 mg per mL, 25 vials of 1 mL
NDC 0008-0077-01, 50 mg per mL, 25 vials of 1 mL

INSERT HERE:
Store at room temperature, approximately 25°C (77°F).

[redacted] AVAILABLE

[redacted] as follows:

NDC 0008-0416-01, 25 mg per mL, 25 TUBES of 1 mL
NDC 0008-0417-01, 50 mg per mL, 25 TUBES of 1 mL

[redacted] Laboratories Inc., Philadelphia PA 19101

[redacted]

333

NDA-00005588

LETTER FROM WYETH TO FDA DATED MAY 3, 1988 (DEFENDANT'S SUMMARY JUDGMENT EXHIBIT F)

RECEIPT COPY

WYETH-AYERST [logo] *LABORATORIES*

P.O. BOX 8299, PHILADELPHIA, PA 19101-1245 • *(215) 688-4400*

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

Stamp: REC'D [Illegible]

May 3, 1988

NDA No. 8-857/S-009

Philip G. Walters, M.D., Acting Director
Division of Surgical-Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Walters:

Reference is made to our approved new drug application no. 8-857 for "Phenergan®, promethazine hydrochloride, Injection" as well as to our September 21, 1981 (S-009) supplemental application, and subsequent amendments, providing package inserts revised to conform to the Federal Register notices relative to content and format labeling requirements for this product.

Reference is also made to your communications of May 26, 1987 and November 13, 1987 which requested additional changes in the text of the labeling covered by this supplemental application.

In response to your letters, we are pleased to provide herewith four draft copies of the revised Phenergan Injection package insert incorporating the changes recommended in your correspondence. Also, we have included additional medically significant information to the proposed text.

We trust that you will find this proposed labeling satisfactory and will so advise us at your earliest convenience.

Sincerely,

WYETH-AYERST LABORATORIES

/s/

Paul V. Uses
Associate Director
Drug Regulatory Affairs

PVU:dlo
25352(4)

WYETH-AYERST [logo] *LABORATORIES*

P.O. BOX 8299, PHILADELPHIA, PA 19101-1245 • *(215) 688-4400*

Division of American Home Products Corporation

August 22, 1988

Phenergan® Injection NDA No. 08-857/S-009

Amplification of Draft Labeling Submitted May 3, 1988

Phenergan® Injection NDA No. 08-857/S-009

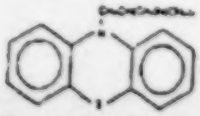
AMPLIFICATION OF DRAFT LABELING SUBMITTED 5/3/88

1. Handwritten notes indicate changes from FDA text, or additional information supplied to improve consistency among Phenergan® package inserts.
2. Highlighted text without explanatory notes indicates changes or additions to clarify the text or to improve the information flow.

Wyeth®
Phenergan®
(promethazine HCl)
Injection

[illegible]

[illegible]



[illegible]

INSERT HERE:
Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S \cdot HCl$ and its molecular weight is 320.88. The pH for the drug product is between 4.0 and 5.5.

[illegible]

Clinical Pharmacology

DELETE THIS PARAGRAPH. SUBSTITUTE THE FOLLOWING:

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

and Usage

[illegible]

[redacted]

END PARAGRAPH WITH:
promethazine or other phenothiazines.

ADD THE FOLLOWING WARNINGS:

Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or in combination with narcotics or local anesthetics which may also affect seizure threshold.

Tot differ slightly in an effort to be consistent with tot for tablet and Suppository dosage forms

[redacted]

The anticholinergic properties of promethazine have resulted in precipitation of acute narrow angle glaucoma, pyloroduodenal obstruction and urinary tract obstruction. Although such conditions have been rare with promethazine, consideration should be given to the risk of these in prescribing promethazine, especially for patients with a known predisposition to these complications such as those with esophageal peptic ulcer or benign prostatic hypertrophy.

Order of these two statements is reversed as compared to FDA letter of March 14, 1985

"There are no data on safety or efficacy of use of promethazine injection to treat an acute asthmatic attack, therefore, such use is not recommended.

"Administration of promethazine has been associated with reported cholestatic jaundice. This should be taken into consideration when interpreting laboratory results and when selecting medication in patients with impaired liver function.

[redacted]

DELETE THESE TWO PARAGRAPHS AND SUBSTITUTE THE INFORMATION FOUND ON THE NEXT PAGE

[redacted]

[redacted]

[redacted]

INADVERTENT INTRAARTERIAL INJECTION

When preparing to give prometharine intravenously, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. There are reports of severe tissue injury, including necrosis with resultant gangrene requiring amputation, following the injection of prometharine, usually in conjunction with other drugs meant for intravenous use. Although the intravenous route was intended in all these cases, arterial or partial arterial placement of the needle is now suspect. The mechanism of producing this injury is uncertain, however animal experiments with other arteriolar irritants suggest that the primary cause may be platelet aggregation and thrombosis starting distal to the site of injection.

The first indication of this problem is usually the patient's complaint of severe pain or a sensation of fiery burning, roughly following the distribution path of the injected artery. At the first complaint of any pain during the intended intravenous injection of prometharine, the injection should be stopped immediately and evaluated for possible arterial placement of the needle. Blanching may be present early, may be transient or may not be noted at all. Mottled cyanosis and dark discoloration usually follow. Pain is usually persistent and the skin temperature distal to the injection site may be decreased.

There is no established treatment that has been shown to be successful in the management of this condition after it occurs. Post injury injection of vasodilators and/or arterial infusion of parenteral fluids are generally regarded as being of no value in altering outcome. Animal experiments and published individual case reports concerned with a variety of arteriolar irritants suggest that one or more of the following may be of benefit in reducing the area of necrosis:

1. Heparinization with continuous intra-arterial injection of heparin proximal to the site of injury until pain and swelling have subsided (up to two weeks).

2. Sympathetic block (or brachial plexus block in the arm), if anticoagulant therapy permits.

3. Intra-arterial glucocorticoid injection at the site of injury, followed by systemic steroids.

4. A recent case report (non-promethazine drug injury) suggests that intra-arterial urokinase may promote fibrinolysis, even if administered late in treatment.

Since prevention is the only method shown to be effective in dealing with this problem, the following points are among those that should be considered in its prophylaxis:

1. Beware of the close proximity of arteries and veins at commonly used injection sites and consider the possibility of aberrant arteries.

2. When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg/ml and at a rate not to exceed 25 mg/minute. Injection into an intravenous infusion set that is known to be running properly should decrease the possibility of inadvertently injecting promethazine intra-arterially. In addition, this results in delivery of a lower concentration of any arteriolar irritant.

3. Subcutaneous swelling near the site of injection calls for discontinuation of promethazine administration and reevaluation of the situation. This sign may be indicative of venous extravasation, which may result in localized necrosis, or it may signify partial arterial placement of the needle or catheter.

4. Be aware that the characteristic bright-red color of arterial blood is discolored by contact with promethazine (italics or different print underlined) so that the aspiration of dark blood does not preclude intra-arterial needle placement.

NDA-00005556

Precautions

GENERAL

Promethazine should be used cautiously in persons with cardiovascular disease or with impairment of bone marrow.

use with caution in patients with lower respiratory disease, including asthma.

INFORMATION FOR PATIENTS

Promethazine may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become unduly drowsy or dizzy from Promethazine therapy. Children should be supervised to avoid potential harm in bike riding or in other hazardous activities.

The concomitant use of alcohol or other central nervous system depressants, including narcotic analgesics, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced.

Patients should be advised to report any involuntary muscle movements or unusual sensitivity to sunlight.

DRUG INTERACTIONS

[illegible]

CNS Depressants - The sedative action of promethazine is additive to the sedative effects of other central-nervous-system depressants, including alcohol, narcotic analgesics, antihistamines, tricyclic antidepressants, phenothiazines, and phenothiazines; therefore, these agents should be avoided or administered in reduced dosage to patients receiving promethazine.

When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

Epinephrine - Although reversal of the vasopressor effect of epinephrine has not been reported with promethazine, in case of promethazine overdose levarterenol or phenylephrine should be administered if a vasopressor is needed. Epinephrine should NOT be used.

MAO Inhibitors - Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAO inhibitors and phenothiazines are used concomitantly. Although such a reaction has not been reported with promethazine, the possibility should be considered.

— This last sentence differs slightly from that suggested in FDA's March 24, 1987 letter in an effort to be consistent with tablet and suppository labeling

— This text is consistent with our tablet and Suppository labeling

DELETE THESE FIVE LINES AND SUBSTITUTE THE INFORMATION FOUND DIRECTLY BELOW THEM

~~LABORATORY~~ TEST INTERACTIONS

The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride.

Pregnancy Tests

Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test

An increase in blood glucose has been reported in cases receiving promethazine.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine, nor are there adequate animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with this drug. Promethazine was nonmutagenic in the Salmonella test system of Ames.

PREGNANCY

Teratogenic Effects—Pregnancy Category C

Teratogenic effects have not been demonstrated in rat-reeding studies at doses of 6.25 and 12.5 mg/kg of promethazine (these doses are [illegible] approximately 2.1 to 4.2 times the maximum recommended total daily dose of promethazine

for a 50-kg subject, depending upon the indication for which the drug is prescribed). Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats produced no effect on these parameters.)

The test used (also incorporates test from previously submitted injection labeling and test from tablets/suppository labeling as requested by FDA

While antihistamines, including promethazine at a daily dosage level of 25 mg/kg intraperitoneally, have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man.

[illegible] with respect to the possible adverse effect on fetal development. Therefore,

Promethazine administered during labor and delivery may inhibit platelet aggregation in the newborn. The clinical significance of this effect is unknown. Test that is highlighted was added in an effort to be consistent with test which was requested by the FDA for suppository labeling (letter of May 26, 1987 - Bateman to Bartlett).

LABOR AND DELIVERY

Phenergan, a suppository dosage form, may be used alone or as an adjunct to narcotic analgesics during labor and delivery. (See "Indications and Usage" and "Dosage and Administration.")

See also "Nonteratogenic Effects."

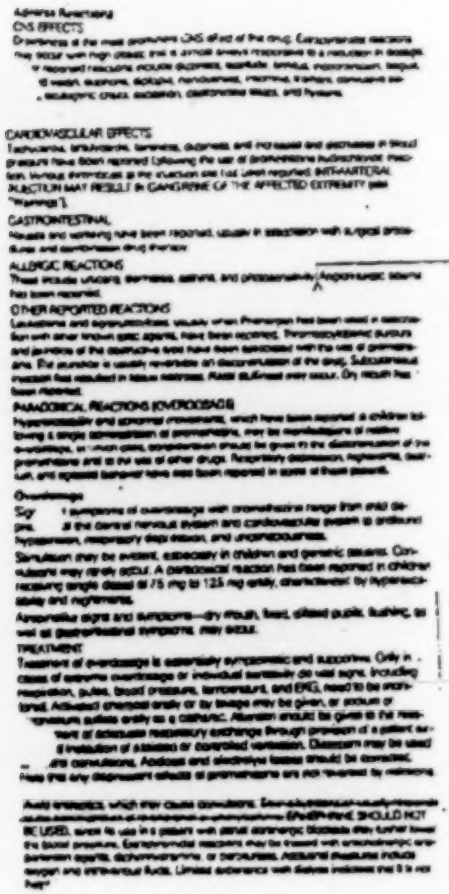
Limited data suggest that the use of Phenergan as a sedative during labor and delivery does not have an appreciable effect on the duration of labor or delivery or in increasing the chances that the newborn will require any type of intervention in the process of delivery when given as recommended. The effect on the later growth, development or functional maturation of the newborn when Phenergan has been used during labor and delivery is unknown.

NURSING MOTHERS

It is not known whether promethazine is excreted in human milk. Caution should be exercised when promethazine is administered to a nursing woman.

Pediatric Use

See Warnings - "Use in Children" and Dosage and Administration



INSERT HERE:
Occurrence of photosensitivity may be a contraindication to further treatment with promethazine or related drugs.

REPLACE THE SECOND SENTENCE WITH THE FOLLOWING:
The treatment of choice for resulting hypotension is administration of intravenous fluids, accompanied by repositioning if indicated. In the event that vasopressors are considered for the management of severe hypotension which does not respond to intravenous fluids and repositioning, the administration of levarterenol or phenylephrine should be considered.

DOSAGE AND ADMINISTRATION

...ateral drug products should be inspected visually ...r particulate matter and discoloration prior to administration whenever solution and container permit.

Injection

Do not use Phenergan if solution is discolored or contains a precipitate.

To avoid the possibility of physical and/or chemical incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

Important Notes on Administration

...Injection into or near a nerve may result in permanent tissue damage.

...

ALLERGIC CONDITIONS

...

...LATION

...

PRE- AND POSTOPERATIVE USE

...

NAUSEA AND VOMITING

...

OBSTETRICS

...

CHILDREN

...

DELETE THIS SENTENCE

ADD THE FOLLOWING SENTENCE AS THE FIRST PARAGRAPH UNDER THE SUBCATEGORY "CHILDREN":
Phenergan Injection should not be used in children less than 2 years of age.
(See Warnings).

How Supplied

...

...

...

INSERT HERE:
Store at room temperature, approximately 25°C (77°F).

AVAILABLE

...as follows:

25 mg per mL, NDC 0008-0416
50 mg per mL, NDC 0008-0417

Wyeth Laboratories Inc., Philadelphia, PA 19101

LETTER FROM WYETH TO FDA DATED AUGUST 6, 1996 (EXHIBIT A TO DEFENDANT'S RENEWED MOTION FOR JUDGMENT AS A MATTER OF LAW EXHIBIT 12)

WYETH-AYERST [logo] *RESEARCH*

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • *(610) 902-3710*
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

[handwritten: SPD-009 BL]

August 6, 1996

Stamp: ORIGINAL/DUPLICATE

Stamp: SUPPL AMENDEMENT

Stamp: "CENTER FOR DRUG
REC'D
AUG 0 8 1996
HFD-570
EVALUATION AND RESEARCH"

NDA No. 8-857/S-009

John Jenkins, M.D., Director
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HDF-570, Room 10B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Dear Mr. Jenkins:

Reference is made to our approved New Drug Application No. 8-857 for Phenergan® (promethazine hydrochloride) Injection as well as to our September 21, 1981 supplemental application (S-009) and subsequent amendments, providing draft package inserts revised to conform with content and format labeling requirements for prescription drug products. Reference is also made to the January 7, 1992 submission by Wyeth-Ayerst of an "administrative record" of S-009, which included the package insert then in use with Phenergan Injection ampul packages. Reference is also made to the telephone call of July 2, 1996 from Dr. Susan Johnson of the Division to the undersigned requesting submission of the current package inserts for Phenergan Injection.

Several minor revisions have occurred in the labeling of Phenergan Injection since the submission in 1992 of the then current ampul insert. Note also that identical inserts were utilized for both Phenergan Tubex® and Phenergan ampuls, except for description and usage information specific to the Tubex Sterile Cartridge Unit, and the sulfite warning, which is specific to the ampul formulation. Attachment 1 contains copies of the current package insert for Phenergan Injection packaged in Tubex® Sterile Cartridge Units, identified as CI 3727-5. The differences between this insert and the insert submitted in 1992 (other than the exceptions described above) are as follows.

Title Area:	Deletion of "Wyeth®"; addition of new log
Description section:	Addition of the statement "Sealed under nitrogen."

How Supplied section:	Deletion of "Wyeth®"; addition of the statement **"Do not use if solution is discolored or contains a precipitate."**
Signature Area:	Addition of new logo; revision of the signature to read: Wyeth Laboratories Inc. A Wyeth-Ayerst Company

The manufacture of Phenergan® Injection ampuls has recently been transferred to another site, ESI (Elkins-Sinn Inc.) in Cherry Hill, New Jersey. ESI, another American Home Products Corporation subsidiary, manufactures the product under their Abbreviated New Drug Application (ANDA) for promethazine hydrochloride injection. The current package insert for the ampuls (Attachment 2; CI 4807-1) utilizes the ANDA labeling, and you will therefore notice the following minor differences between this insert and the labeling of the NDA (Tubex®) product (other than the exceptions described above).

Description section:	Begins with an additional statement which reads "Promethazine hydrochloride Injection, USP is a sterile solution for deep intramuscular or intravenous administration." Addition of molecular weight and chemical formula
Clinical Pharmacology:	This heading is used instead of "Actions"
Indications and Usage:	This heading is used instead of "Indications"

Contraindications:	In the first sentence, there is a comma between the words "sedative" and "hypnotics"
Warnings:	Under "Use in Children", the second paragraph (which begins "Caution should be exercised...") is bolded
Dosage and Administration:	The first and second sentences of the second paragraph are bolded
Management of Overdosage:	The sentence which begins "Parenteral drug products should be inspected..." appears (in bold) at the end of this section; whereas it appears at the end of the "Dosage and Administration" section in the Tubex insert."
How Supplied:	The subheading "Storage" does not appear in the Tubex insert
	The ampul insert states **"Keep covered in carton until time of use;"** whereas the Tubex insert states **"Use carton to protect contents from light."**
	The "Do not use if..." and "Store at..." statements are bolded in the Tubex® insert
	The storage temperature range (15°-30°C) in the ampul insert reflects the ANDA labeling
How Supplied (continued):	The "ALSO AVAILABLE" subsection of the ampul insert describes Tubex, while the Tubex insert de-

scribes ampuls.

For your information, we have also included the package insert utilized for the ampuls before the transition to the ANDA product (Attachment 3: CI 3900-3).

Please note that changes to the labeling of the NDA Phenergan Injection product resulting from supplement 009 will be incorporated by ESI into the labeling of the Phenergan ampul product and reported to the Office of Generic Drugs in an appropriate manner.

I hope the enclosed material will facilitate the approval supplement 009 at your earliest convenience. If you have any questions regarding this submission, please contact the undersigned at (610) 902-3761 or Mr. John Seneca at (610) 902-3724.

Sincerely,

WYETH-AYERST LABORATORIES

/s/

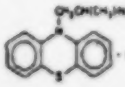
James J. O'Shaughnessy
Associate Director
U. S. Regulatory Affairs

JOS:JS:\a:1081.phe

ATTACHMENT 1

Phenergan®
(promethazine HCl)
Injection

Description
Promethazine HCl (10*H*-phenothiazine-10-ethanamine, *N,N,α*-trimethyl-, monohydrochloride) has the following structural formula:



Each mL of the TUBEX® and TUBEX® BLUNT POINTE™ Sterile Cartridge Units contains either 25 or 50 mg promethazine hydrochloride with 0.1 mg edetate disodium, 0.04 mg calcium chloride, not more than 5 mg monothioglycerol and 5 mg phenol with sodium acetate-acetic acid buffer. Sealed under nitrogen.

Actions
Promethazine hydrochloride, a phenothiazine derivative, possesses antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects. The duration of action is generally from four to six hours. The major side reaction of this drug is sedation. As an antihistamine, it acts by competitive antagonism but does not block the release of histamine. It antagonizes in varying degrees most but not all of the pharmacological effects of histamine.

Indications
The injectable form of promethazine hydrochloride is indicated for the following conditions:
1. Amelioration of allergic reactions to blood or plasma.
2. In anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
4. Active treatment of motion sickness.
5. Preoperative, postoperative, and obstetric (during labor) sedation.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
8. For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
9. Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery, and poor-risk patients, with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia.

Contraindications
Promethazine is contraindicated in comatose states, in patients who have received large amounts of central-nervous-system depressants (alcohol, sedative hypnotics, including barbiturates, general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc.), and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine.

Under no circumstances should promethazine be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see "Warnings").

Phenergan injection should not be given by the subcutaneous route; evidence of chemical irritation has been noted, and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

Warnings
Promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The concomitant use of alcohol, sedative hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers or other central-nervous-system depressants may have an additive sedative effect. Patients should be warned accordingly.

USAGE IN PREGNANCY
The safe use of promethazine has not been established with respect to the possible adverse effects upon fetal development. Therefore, the need for the use of this drug during pregnancy should be weighed against the possible but unknown hazards to the developing fetus.

USE IN CHILDREN
Excessively large dosages of antihistamines, including promethazine, in children may cause hallucinations, convulsions, and sudden death. In children who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of promethazine hydrochloride injection.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN TO CHILDREN. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN CHILDREN, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN SHOULD BE AVOIDED IN CHILDREN WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME, OR OTHER HEPATIC DISEASES.

USE IN THE ELDERLY (APPROXIMATELY 60 YEARS OR OLDER)
Since therapeutic requirements for sedative drugs tend to be less in elderly patients, the dosage of Phenergan should be reduced for these patients.

OTHER CONSIDERATIONS
Drugs having anticholinergic properties should be used with caution in patients with asthmatic attack, narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.

Phenergan should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known toxic agents.

INADVERTENT INTRA-ARTERIAL INJECTION
Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of promethazine, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported, but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of this condition after it occurs, although sympathetic block and heparinization are commonly employed during the acute management because of the results of animal experiments with other known arterial irritants. Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with promethazine. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg per mL, and at a rate not to exceed 25 mg per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended intravenous injection of promethazine, the injection should immediately be stopped to provide for evaluation of possible arterial placement or perivascular extravasation.

Precautions
Promethazine may significantly affect the actions of other drugs. It may increase, prolong, or intensify the sedative action of central-nervous-system depressants, such as alcohol, sedative hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain. Promethazine should be used cautiously in persons with cardiovascular disease or impairment of liver function.

Although reversal of the vasopressor effect of epinephrine has not been reported with promethazine, the possibility should be considered in case of promethazine overdose.

Adverse Reactions
CNS EFFECTS
Drowsiness is the most prominent CNS effect of this drug. Extrapyramidal reactions may occur with high doses; this is almost always responsive to a reduction in dosage. Other reported reactions include dizziness, lassitude, tinnitus, incoordination, fatigue, blurred vision, euphoria, diplopia, nervousness, insomnia, tremors, convulsive seizures, oculogyric crises, excitation, catatonic-like states, and hysteria.

CARDIOVASCULAR EFFECTS
Tachycardia, bradycardia, faintness, dizziness, and increases and decreases in blood pressure have been reported following the use of promethazine hydrochloride injection. Venous thrombosis at the injection site has been reported. INTRA-ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see "Warnings").

GASTROINTESTINAL
Nausea and vomiting have been reported, usually in association with surgical procedures and combination drug therapy.

ALLERGIC REACTIONS
These include urticaria, dermatitis, asthma, and photosensitivity. Angioneurotic edema has been reported.

OTHER REPORTED REACTIONS
Leukopenia and agranulocytosis, usually when Phenergan has been used in association with other known toxic agents, have been reported. Thrombocytopenic purpura and jaundice of the obstructive type have been associated with the use of promethazine. The jaundice is usually reversible on discontinuation of the drug. Subcutaneous injection has resulted in tissue necrosis. Nasal stuffiness may occur. Dry mouth has been reported.

LABORATORY TESTS
The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:

Pregnancy Tests — Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test — An increase in glucose tolerance has been reported in patients receiving promethazine hydrochloride.

PARADOXICAL REACTIONS (OVERDOSAGE)
Hyperexcitability and abnormal movements, which have been reported in children following a single administration of promethazine, may be manifestations of relative overdosage, in which case, consideration should be given to the discontinuation of the promethazine and to the use of other drugs. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

Drug Interactions
NARCOTICS AND BARBITURATES
The CNS-depressant effects of narcotics are additive with promethazine hydrochloride.

Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly. Although such a reaction has not been reported with promethazine, the possibility should be considered.

Dosage and Administration

The preferred parenteral route of administration for promethazine hydrochloride is by deep intramuscular injection. The proper intravenous administration of this product is well tolerated, but use of this route is not without some hazard.

INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY [see "Warnings"]. SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (see "Contraindications"). When used intravenously, promethazine hydrochloride should be given in concentration no greater than 25 mg/mL at a rate not to exceed 25 mg per minute; it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

The TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is suitable for substances to be administered intravenously only. It is intended for use with injection sets specifically manufactured as "needle-less" injection systems. TUBEX® BLUNT POINTE™ is compatible with Abbott's LifeShield® preplerced reseal injection site, Baxter's InterLink® Injection Site, and B. Braun Medical's SafeSite® Reflux Valve. Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" system. It is also intended for admixture with, and convenient administration of, various medicaments when using Drug Vial Adapters for "needle-less" injection systems.

The TUBEX® Sterile Cartridge-Needle Unit is suitable for substances to be administered intravenously or intramuscularly.

ALLERGIC CONDITIONS

The average adult dose is 25 mg. This dose may be repeated within two hours if necessary, but continued therapy, if indicated, should be via the oral route as soon as existing circumstances permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The average adult dose for amelioration of allergic reactions to blood or plasma is 25 mg.

SEDATION

In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of promethazine hydrochloride.

PRE- AND POSTOPERATIVE USE

As an adjunct to pre- or postoperative medication, 25 to 50 mg of promethazine hydrochloride in adults may be combined with appropriately reduced doses of analgesics and atropine-like drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

NAUSEA AND VOMITING

For control of nausea and vomiting, the usual adult dose is 12.5 to 25 mg, not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or intravenously and dosage of analgesics and barbiturates reduced accordingly.

OBSTETRICS

Phenergan in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25 to 75 mg (average dose, 50 mg) promethazine hydrochloride may be given intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. Amnesic agents may be administered as necessary. If necessary, Phenergan with a reduced dose of analgesic may be repeated once or twice at four-hour intervals in the course of a normal labor. A maximum total dose of 100 mg of Phenergan may be administered during a 24-hour period to patients in labor.

CHILDREN

In children under the age of 12 years, the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication, the suggested dose is 0.5 mg per lb. of body weight in combination with an equal dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in children.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Management of Overdosage

Signs and symptoms of overdosage range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness. Stimulation may be evident, especially in children and geriatric patients. Atropine-like signs and symptoms — dry mouth, fixed, dilated pupils, flushing, etc., as well as gastrointestinal symptoms, may occur. The treatment of overdosage is essentially symptomatic and supportive. Early gastric lavage may be beneficial if promethazine has been taken orally. Centrally acting emetics are of little use.

Avoid analeptics, which may cause convulsions. Severe hypotension usually responds to the administration of levarterenol or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since its use in a patient with partial adrenergic blockage may further lower the blood pressure. Extrapyramidal reactions may be treated with antiCholinergic antiparkinson agents, diphenhydramine, or barbiturates. Additional measures include oxygen and intravenous fluids. Limited experience with dialysis indicates that it is not helpful.

How Supplied

Phenergan® (promethazine HCl) Injection is available in the following dosage strengths in TUBEX® BLUNT POINTE™ Sterile Cartridge Units and Sterile Cartridge-Needle Units, packaged in boxes of 10 TUBEX as follows:

25 mg per mL, NDC 3008-0416-50, 1 mL size Blunt Pointe™.

25 mg per mL, NDC 3008-0416-01, 1 mL size (22 gauge x 1-1/4 inch needle).

50 mg per mL, NDC 3008-0417-01, 1 mL size (22 gauge x 1-1/4 inch needle).

Store at room temperature, between 15°-25° C (59°-77° F).

Protect from light.

Use carton to protect contents from light.

Do not use if solution is discolored or contains a precipitate.

ALSO AVAILABLE:

Ampuls of 1 mL, in packages of 25 and 100, as follows:

25 mg per mL, NDC 0008-0063-01

50 mg per mL, NDC 0008-0476-01

* * *

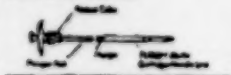
AND TUBEX FAST-TRAK SYRINGE HAVE BEEN DISCONTINUED AND REPLACED BY THE TUBEX INJECTOR. EXCHANGE OF THESE DISCONTINUED SYRINGES IS AVAILABLE, FREE OF CHARGE, FROM YOUR WYETH-AYERST SALES REPRESENTATIVE, OR FROM WYETH-AYERST DIRECTLY. FOR LOADING AND UNLOADING INFORMATION ON THESE DISCONTINUED SYRINGES, CONTACT THE MEDICAL AFFAIRS DEPARTMENT, AT WYETH-AYERST LABORATORIES, P.O. BOX 8299, PHILADELPHIA, PA 19101.

TUBEX® Injector

NOTE: The TUBEX® Injector is reusable; do not discard.

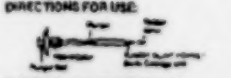
TUBEX® Sterile Cartridge-Needle Unit

DIRECTIONS FOR USE:

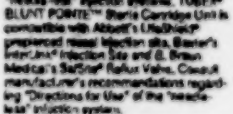


TUBEX® BLUNT POINTE™ Sterile Cartridge Unit

DIRECTIONS FOR USE:



TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is intended for use with injection sets specifically manufactured as "needle-less" injection systems. TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is compatible with Abbott's LifeShield® preplerced reseal injection site, Baxter's InterLink® Injection Site and B. Braun Medical's SafeSite® Reflux Valve. Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" injection system.



To load a TUBEX® Sterile Cartridge Unit into the TUBEX® injector:

1. Turn the ribbed collar to the "OPEN" position until it stops.

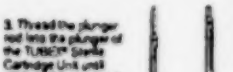
TUBEX® Sterile Cartridge-Needle Unit

TUBEX® BLUNT POINTE™ Sterile Cartridge Unit

2. Hold the injector with the open end up and fully insert the TUBEX® Sterile Cartridge Unit. Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

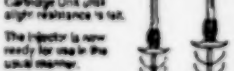
3. Thread the plunger rod into the plunger of the TUBEX® Sterile Cartridge Unit until slight resistance is felt.

The injector is now ready for use in the usual manner.

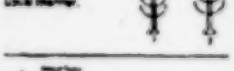


To load an E.S.I. DOSETTE® Sterile Cartridge-Needle Unit into the TUBEX® Injector:

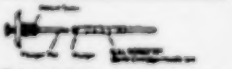
1. Turn the ribbed collar to the "OPEN" position until it stops.



2. Hold the injector with the open end up and fully insert the E.S.I. DOSETTE® Sterile Cartridge-Needle Unit. Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.



3. Thread the plunger rod into the plunger of the E.S.I. DOSETTE® Sterile Cartridge-Needle Unit until slight resistance is felt.



4. Engage the needle cap assembly by pulling the cap down over the silver cartridge hub. The needle is fully engaged when the silver hub is completely covered.

The injector is now ready for use in the usual manner.

To administer TUBEX®/DOSETTE® Sterile Cartridge-Needle Units:

Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely; twist and pull. Introduce needle into patient, aspirate by pulling back slightly on the plunger, and inject.

To administer TUBEX® BLUNT POINTE™ Sterile Cartridge Units "Needle-less" IV set administration is similar to administration with conventional syringes. Remove rubber cover by grasping it securely, twist and pull. For B. Braun Medical's SafeSite® Reflux Valves, aseptically swab the luer slip fitting of the BLUNT POINTE™ sterile cartridge tip assembly with a sterile, individually wrapped, saturated 70% Isopropyl Alcohol swab. This action will remove the lubricant coating from the tip to facilitate a tight seal. Introduce TUBEX® BLUNT POINTE™ Sterile Cartridge Unit into the "needle-less" IV set as per manufacturer's "Directions for Use."

To remove the empty TUBEX®/DOSETTE® Cartridge Unit and dispose into a vertical disposal container:

1. Do not recap the needle/point. Disengage the plunger rod.

2. Hold the injector, needle/point down, over a vertical disposal container and loosen the ribbed collar. TUBEX®/DOSETTE® Cartridge Unit will drop into the container.

3. Discard the cover.

To remove the empty TUBEX®/DOSETTE® Cartridge Unit and dispose into a horizontal (mailbox) disposal container:

1. Do not recap the needle/point. Disengage the plunger rod.

2. Open the horizontal (mailbox) disposal container, insert TUBEX®/DOSETTE® Cartridge Unit, needle/point pointing down, halfway into container. Close the container lid on cartridge. Loosen ribbed collar. TUBEX®/DOSETTE® Cartridge Unit will drop into the container.

3. Discard the cover.

The TUBEX® injector is reusable and should not be discarded.

Used TUBEX®/DOSETTE® Cartridge Units should not be employed for parenteral injections or as multiple-dose containers. They are intended to be used only once and discarded.

NOTE: Any graduation markings on TUBEX®/DOSETTE® Sterile Cartridge Units are to be used only as a guide in mixing, withdrawing, or administering measured doses.

Wyeth-Ayerst does not recommend and will not accept responsibility for the use of any cartridge-needle units or needle-less units other than TUBEX® or E.S.I. DOSETTE® Cartridge Units in the TUBEX® Injector.

INTERNAL WYETH MEMORANDUM DATED JANUARY 30, 1997 (DEFENDANT'S TRIAL EXHIBIT U)

[logo]

INTERNAL CORRESPONDENCE

to File	from James O'Shaughnessy (initials)
company	company W-AR located 170/2
subject Phenergan® Injection Pending Supplements	date January 30, 1997

Stamp: CONFIDENTIAL

On January 29, 1997, I spoke with Ms. Beverly Gallauresi of the Division of Pulmonary Drug Products (DPDP) regarding the following pending supplemental applications for Phenergan Injection.

* * *

NDA No. 8-857/S-009
Labeling Supplement

This supplement was initially filed in 1981. There have been numerous amendments and submissions of draft labeling and supportive documentation over the years. In June 1996, Wyeth-Ayerst was asked to prepare a narrative outlining the differences in the text of the currently approved package insert and any text changes since 1992. During the remainder of 1996, the DPDP consistently advised that the labeling review was nearing an end.

During today's conversation, Ms. Gallauresi indicated that the labeling review is complete. However, because it has taken the DPDP so long to complete the review, they are taking extra care to make sure they have dotted every "i" and crossed every "t." She advised me that a letter is circulating within the DPDP for final review and comments. Ms. Gallauresi said she hoped this letter could be FAXed to us in the very near future, however, she could not guarantee that this would happen before Friday, February 7, 1997.

JOS:am

cc: Mr. Bathish
Dr. Bernady
Dr. DeVries
Mr. Seneca
Mr. Victoria

LETTER FROM FDA TO WYETH DATED FEBRUARY 21, 1997 (DEFENDANT'S TRIAL EXHIBIT O)

[logo]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

Stamp: CONFIDENTIAL

Stamp: FEB 21 1997

Stamp: RECEIVED
FEB 26 1997
Mr. J. O'Shaughnessy

cc: JNB, KFB, CSC, VDV,
JOS, JS, JRV, GRO, Log

NDA 8-857/S-009

Wyeth-Ayerst
P.O. Box 8299
Philadelphia, PA 19101-8299

Attention: James J. O'Shaughnessy
Associate Director
U.S. Regulatory Affairs

Dear Mr. O'Shaughnessy:

Reference is made to your supplemental new drug application dated September 21, 1981, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenergan (promethazine hydrochloride) Injection.

We acknowledge receipt of your amendments dated May 3, 1988, February 1, March 1, and May 15, 1989, January 7, 1992, and August 6, 1996.

We have completed the review of this supplemental application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as follows.

The following comments are provided regarding the versions of the Phenergan Tubex and Ampul labeling submitted in the August 6, 1996 amendment. Please note that the term "current labeling" refers to these versions.

1. Identical inserts should be utilized for both Phenergan Tubex and Phenergan Ampuls, except for description and usage information specific to the Tubex Sterile Cartridge Unit and the sulfite warning, which is specific to the ampul formulation.

2. The format for the trade name should be "Phenergan (promethazine HCL) Injection" and should be used consistently for both the tubex and ampul products. Within the package inserts, the term "promethazine hydrochloride" or "promethazine HCL" is appropriate for the DESCRIPTION and the CLINICAL PHARMACOLOGY sections, however, the trade name should be used consistently throughout the remainder of the labeling to refer to the drug product.

3. The DESCRIPTION section of both the tubex and ampul inserts should include the molecular weight, empirical formula and pH. Both inserts

should state that promethazine hydrochloride is a racemic compound and the Chemical name should be modified to read "... monohydrochloride±)."

4. The DESCRIPTION section should include a statement which indicates that the drug is "sterile and pyrogen free" and that it is "sealed under nitrogen."

5. The following statement should be added to the DESCRIPTION section. "Phenergan (promethazine HCL) Injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed."

6. The CLINICAL PHARMACOLOGY section should be titled as such and should read as follows.

   Promethazine hydrochloride is a phenothiazine derivative which possesses antihistaminic, sedative, antimotion-sickness, antiemetic and anticholinergic effects. Promethazine is a competitive H_1 receptor antagonist, but does not block the release of histamine. Structural differences from the neuroleptic phenothiazines results in its relative lack (1/10) of dopamine antagonist properties. In therapeutic doses, promethazine hydrochloride produces no significant effects on the cardiovascular system. Clinical effects are generally apparent within 5 minutes of an intravenous injection and within 20 minutes of an intramuscular injection. Duration of action is four to six hours, although effects may persist up to 12 hours. Promethazine hydrochloride is metabolized in the liver, with

the sulfoxides of promethazine and N-desmethylpromethazine being the predominant metabolites appearing in the urine.

7. The INDICATIONS AND USAGE section should be titled as such in both the tubex and ampul labeling.

8. It is recommended that the sequence of indications in the INDICATIONS AND USAGE section be ordered in the same manner as the DOSAGE AND ADMINISTRATION section, or vice versa.

9. The concurrent use of promethazine with other phenothiazine drugs should be limited, however, it is not clear that this interaction is strictly contraindicated as the current CONTRAINDICATIONS section states. These additive interactions may be identified in the Drug Interactions subsection of the PRECAUTIONS section:

10. The WARNINGS section should be modified to read as follows.

SULFITE SENSITIVITY—

a. Phenergan HCL Injection (ampuls only) contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthma episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

b. **CNS Depression**—Phenergan Injection may impair the mental and physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central nervous system depressants such as alcohol, sedative hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. (See Information for Patients).

c. **Lower Seizure Threshold**—Phenergan Injection may lower seizure threshold and should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

d. **Bone Marrow Depression**—Phenergan Injection should be used with caution in patients with bone marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known marrow toxic agents.

e. **Use in Children**—Retain verbiage in current label. Add "Phenergan Injection is not recommended for use in children less than two years of age."

f. **Inadvertent Intra-arterial Injection**—Retain verbiage in current label.

g. **Visual Inspection**—This product is light sensitive and should be inspected before

use and discarded if either color particulate is observed.

11. Information regarding use in the elderly and use in pregnancy may be moved to the PRECAUTIONS section. The "Other Considerations" subsection can be removed.

12. The PRECAUTIONS section should be divided into subsections as follows:

General

Drugs having anticholinergic properties should be used with caution in patients with narrow angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction and bladder-neck obstruction.

Phenergan Injection should be used with caution in persons with cardiovascular disease or impairment of liver function.

Information for Patients

Phenergan Injection may impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol, sedative hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. with Phenergan Injection may enhance the impairment. Persistent or worsening pain or burning at the injection site should be reported immediately. Avoid prolonged exposure to the sun.

Drug Interactions

This section should be relocated from its current position in the labeling and modified as specified below.

CNS Depressants—Phenergan Injection may increase, prolong or intensify the sedative action of central nervous system depressants such as alcohol, sedative hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. When given concomitantly with Phenergan Injection, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of Phenergan Injection relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

Epinephrine—Although reversal of the vasopressor effect of epinephrine has not been reported with Phenergan Injection, it is recommended that epinephrine NOT be used in the case of Phenergan Injection overdose.

Anticholinergics—Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

Monoamine Oxidase (MAO) Inhibitors—retain information currently in tubex labeling.

Laboratory Test Interactions

Information from the ADVERSE REACTIONS section of the current labeling should be relocated in this subsection.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long term animal studies have not been performed to assess the carcinogenic potential of Phenergan Injection, nor are there other animal or human data concerning carcinogenicity, mutagenicity or impairment of fertility. Phenergan Injection was nonmutagenic in the Ames Salmonella test system.

Teratogenic Effects—Pregnancy Category C

Teratogenic effects have not been demonstrated in rat feeding studies at doses of 6.25 and 12.5 mg/kg (approximately 2.1 and 4.2 times the maximum recommended human daily dose) of Phenergan Injection. Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats.

There are no adequate and well-controlled studies of Phenergan Injection in pregnant women. Because animal reproduction studies are not always predictive of human response, Phenergan Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adequate studies to determine the action of the drug on parturition, lactation and development of the animal neonate have not been conducted.

Use in Labor and Delivery

Phenergan Injection may be used alone or as an adjunct to narcotic analgesics during labor (See DOSAGE AND ADMINISTRATION). Limited data suggest that use of Phenergan Injection during labor and delivery does not have an

appreciable effect on the duration of labor or delivery and does not increase the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown.

Nursing Mothers

It is not known whether Phenergan Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Phenergan Injection is administered to a nursing woman.

Pediatrics

Phenergan Injection should be used with caution in pediatric patients. See WARNINGS Section.

Use in the Elderly (Approximately 60 years or older)

Since therapeutic requirements for sedative drugs tend to be less in geriatric patients, the dosage should be reduced for these patients.

13. The following comments pertain to the ADVERSE REACTIONS section.

    a. The Laboratory Tests subsection should be removed from the ADVERSE REACTIONS section.

    b. In a recent review of the Spontaneous Reporting System database, it was determined that the term "hallucinations" was reported with significant frequency and we believe that the pharmacologic activity of promethazine is such that a causal relationship may be inferred from these data. This

term is currently included in the package insert under WARNINGS, subsection, "Use in Children." We request that it also be added to the ADVERSE REACTIONS, subsection, "CNS Effects."

14. The OVERDOSAGE section should follow the ADVERSE REACTIONS section and should be titled consistently. The remainder of the section is acceptable.

15. The DOSAGE AND ADMINISTRATION section should be modified as follows,

    a. The sentence which ends "...without some hazard." should be followed by "Not for subcutaneous administration."

    b. The sentence which begins "Inadvertent intra-arterial injection ..." should appear in bold. The statement which follows, regarding rate of administration, should be offset in a separate paragraph.

    c. The subsection titled "Children" should contain the statement "Phenergan Injection is not recommended for use in children less than two years of age."

    d. The sentence "Parenteral drug products should be inspected visually ..." should also appear in bold and should be moved to the beginning of the DOSAGE AND ADMINISTRATION section.

16. Regarding the tubex product, the instructions for use refer to a "Tubex injector." This device should be described in the HOW SUPPLIED section.

17. Both Ampuls and Tubex boxes, 25 and 50 mg strength, should describe route of injection as 25 mg—IV or IM, 50 mg—IM only.

Please submit 16 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

If you have any questions, please contact Ms. Beverly Gallauresi, Project Manager, at (301) 827-1054.

Sincerely yours,

/s/

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

LETTER FROM WYETH TO FDA DATED MAY 8, 1998 (DEFENDANT'S TRIAL EXHIBIT N)

WYETH-AYERST [logo] *RESEARCH*

U.S. REGULATORY AFFAIRS

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

May 8, 1998

NDA 8-857/S-009
Phenergan® Injection

John Jenkins, M.D., Director
Division of Pulmonary Drug Products (HDF-570)
Center for Drug Evaluation and Research
Document Control Room 10B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

Dear Mr. Jenkins:

Reference is made to our approved New Drug Application No. 8-857 for Phenergan® (promethazine hydrochloride) Injection as well as to our September 21, 1981 supplemental application (S-009), and subsequent amendments, providing draft package inserts revised to conform with content and format labeling requirements for prescription drug products. Reference is also made to the February 21, 1997 letter from the Division of Pulmonary Drug Products (DPDP) advising us that S-009 is "approvable," and requesting the submission revised final printed labeling.

The purpose of this communication is to submit the enclosed copies (four) of draft package insert labeling for Phenergan® Injection in Tubex® (Attachment 1) and Phenergan® Injection ampuls (Attachment 2) that has been revised in accordance with the comments contained in the DPDP's February 21, 1997 letter. Please note however the following modifications:

1) Under "CLINICAL PHARMACOLOGY," information has been added on the mean plasma half-life of promethazine following intravenous and intramuscular administration. The supporting references for this information are included as Attachment 3.

2) Under "WARNINGS—Use in Pediatric Patients," the requested statement, "Phenergan Injection is not recommended for use in pediatric patient less than two years of age," has been added in bold, upper case type at the beginning of the section, followed by the bolded paragraph which begins "CAUTION SHOULD BE EXERCISED..."

3) Under "WARNINGS," we propose to retain a section entitled "Other Considerations" containing the following text: "Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea" and "Administration of promethazine has been associated with reported cholestatic jaundice." These statements were proposed in the draft labeling previously submitted; they appear in the current Phenergan Tablets and Suppositories package insert and we believe they are appropriate for the labeling of the injection dosage form.

4) Under "Information for Patients," we propose to retain the phrase "cause marked drowsiness" in the

first sentence (ie., "Phenergan Injection may cause marked drowsiness or impair..."). We also propose to include the statements "Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities" and "Patients should be advised to report any involuntary muscle movements." These statements were proposed in the draft labeling previously submitted; they appear in the current Phenergan Tablets and Suppositories package insert and we believe they are appropriate for the labeling of the injection dosage form.

5) Under "PRECAUTIONS—Pregnancy," we propose to include a subsection titled "Nonteratogenic Effects" with the following text: "Phenergan Injection received within two weeks of delivery may inhibit platelet aggregation in the newborn." This statement was proposed in the draft labeling previously submitted; it appears in the current Phenergan Tablets and Suppositories package insert and we believe it is appropriate for the labeling of the injection dosage form.

6) Under "PRECAUTIONS—Labor and Delivery," the statement "(See also Nonteratogenic Effects)" has been added.

7) Editorial or similarly minor changes have been made throughout the insert, e.g., the word "children" has been replaced with "pediatric patients" where appropriate.

The "OVERDOSAGE" and "DOSAGE AND ADMINISTRATION" sections have been revised to incorporate the recommendations in the February 21, 1997 "approvable" letter, as well as the revisions proposed in S-009 and subsequent amendments. We be-

lieve this reflects the intent of the comments contained in the "approvable" letter with respect to these sections.

In order to facilitate the Agency's review of the modifications described above, we are submitting draft, rather than final printed labeling. The draft labeling consists of work processing copies of the current package inserts for Phenergan Injection in Tubex and Phenergan Injection ampuls which show the changes by means of shading (new text) and strikeout (deleted text). Please note that the current insert for Phenergan Injection in Tubex has undergone a minor revision since the submission of the then current insert on August 6, 1996, ie., the "±" symbol has been added to the chemical name under "DESCRIPTION."

We hope you will find the enclosed labeling satisfactory and will so advise us at your earliest convenience. If you have any questions regarding this submission, please contact the undersigned at 610-902-3775 (fax 610-964-5972) or Mr. John Seneca at 610-902-3724.

Sincerely,

WYETH-AYERST LABORATORIES

/s/

Nanette E. Holston
Manager
U. S. Regulatory Affairs

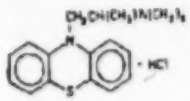
* * *

BEST AVAILABLE COPY

Phenergan®
(promethazine HCl)
Injection

DESCRIPTION

Phenergan (promethazine HCl) Injection is a sterile, pyrogen-free solution for deep intramuscular or intravenous administration. Promethazine HCl (10*H*-phenothiazine-10-ethanamine, *N,N,α*-trimethyl-, monohydrochloride, (±)-) is a racemic compound and has the following structural formula:



$C_{17}H_{20}CN_2S$ MW=320.89

Each mL of the **TUBEX®** and **TUBEX® BLUNT POINTE™** Sterile Cartridge Units contains either 25 or 50 mg promethazine ~~hydrochloride~~ HCl with 0.1 mg edetate disodium, 0.04 mg calcium chloride, not more than 5 mg monothioglycerol, and 5 mg phenol in Water for Injection. The pH range is 4.0 to 5.5, buffered with sodium acetate-acetic acid ~~buffer~~, and it is sealed under nitrogen.

Phenergan (promethazine HCl) Injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

~~Actions~~ CLINICAL PHARMACOLOGY

Promethazine ~~hydrochloride~~ HCl is a phenothiazine derivative which possesses antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects. ~~The major side reaction of this drug is sedation. As an antihistamine, it acts by competitive antagonism but does not block the release of histamine. It antagonizes in varying degrees most but not all of the pharmacological effects of histamine.~~ Promethazine is a competitive H_1 receptor antagonist, but does not block the release of histamine. Structural differences from the neuroleptic phenothiazines results in relatively low (1/10) of dopamine antagonist properties. In therapeutic doses, promethazine HCl produces no significant effects on the cardiovascular system. Clinical effects are generally apparent within 5 minutes of an intravenous injection and within 20 minutes of intramuscular injection. The duration of action is ~~generally~~ from four to six hours, although effects may persist up to 12 hours. Promethazine HCl is metabolized in the liver, with the sulfoxides of promethazine and N-desmethylpromethazine being the predominant metabolites appearing in the urine. Following intravenous administration in healthy volunteers, the plasma half-life for promethazine has been reported to range from 9 to 16 hours. [1] The mean plasma half-life for promethazine after intramuscular administration in healthy volunteers has been reported to be 9.8±3.4 hours. [2]

NDA-00001020

INDICATIONS AND USAGE

~~The injectable form of promethazine hydrochloride~~ Phenergan Injection is indicated for the following conditions:

1. Amelioration of allergic reactions to blood or plasma.
2. In anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
~~8~~ 4. For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
~~4~~ 5. Active treatment of motion sickness.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
~~5~~ 8. Preoperative, postoperative, and obstetric (during labor) sedation.
9. Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery, and poor-risk patients, with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia.

CONTRAINDICATIONS

~~Promethazine~~ Phenergan Injection is contraindicated in comatose states~~, in patients who have received large amounts of central nervous system depressants (alcohol, sedative hypnotics, including barbiturates, general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc.)~~; and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine or other phenothiazines.

Under no circumstances should ~~promethazine~~ Phenergan Injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see "WARNINGS—Inadvertent Intra-arterial Injection").

Phenergan Injection should not be given by the subcutaneous route; evidence of chemical irritation has been noted, and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

WARNINGS

CNS Depression

~~Promethazine~~ Phenergan Injection may impair the mental and/~~or~~ physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. (see "PRECAUTIONS—Information for Patients"). ~~or other central nervous system depressants may have an additive sedative effect.~~

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~~Patients should be warned accordingly.~~

Lower Seizure Threshold

Phenergan Injection may lower seizure threshold and should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

Bone-Marrow Depression

Phenergan Injection should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known marrow-toxic agents.

~~USAGE IN PREGNANCY~~

~~The safe use of promethazine has not been established with respect to the possible adverse effects upon fetal development. Therefore, the need for the use of this drug during pregnancy should be weighed against the possible but unknown hazards to the developing fetus.~~

Use in ~~CHILDREN~~ Pediatric Patients

PHENERGAN INJECTION IS NOT RECOMMENDED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN INJECTION TO ~~CHILDREN~~ PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN ~~CHILDREN~~ PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN INJECTION ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN INJECTION SHOULD BE AVOIDED IN ~~CHILDREN~~ PEDIATRIC PATIENTS WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASES.

Excessively large dosages of antihistamines, including ~~promethazine~~ Phenergan Injection, in ~~children~~ pediatric patients may cause hallucinations, convulsions, and sudden death. In ~~children~~ pediatric patients who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of ~~promethazine hydrochloride~~ Phenergan Injection.

~~USE IN THE ELDERLY (APPROXIMATELY 60 YEARS OR OLDER)~~ [TEXT RELOCATED TO PRECAUTIONS]

~~Since therapeutic requirements for sedative drugs tend to be less in elderly patients, the dosage of Phenergan should be reduced for these patients.~~

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Inadvertent Intra-arterial Injection

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of ~~promethazine~~ Phenergan Injection, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of this condition after it occurs, although sympathetic block and heparinization are commonly employed during the acute management because of the results of animal experiments with other known arteriolar irritants. Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with ~~promethazine~~ Phenergan Injection. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

When used intravenously, ~~promethazine hydrochloride~~ Phenergan Injection should be given in a concentration no greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended intravenous injection of ~~promethazine~~ Phenergan Injection, the injection should be stopped immediately to provide for evaluation of possible arterial placement or perivascular extravasation.

Visual Inspection

This product is light sensitive and should be inspected before use and discarded if either color or particulate is observed.

Other Considerations

Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea.

~~Administration of promethazine has been associated with reported cholestatic jaundice.~~

~~Drugs having anticholinergic properties should be used with caution in patients with asthmatic attack, narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.~~ [TEXT RELOCATED TO PRECAUTIONS—GENERAL]

PRECAUTIONS

~~Promethazine may significantly affect the actions of other drugs.~~

General

Drugs having anticholinergic properties should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction. [TEXT RELOCATED FROM WARNINGS—OTHER CONSIDERATIONS]

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~~Promethazine~~ Phenergan Injection should be used cautiously in persons with cardiovascular disease or impairment of liver function.

Information for Patients

Phenergan Injection may cause marked drowsiness or impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. with Phenergan Injection may enhance impairment. Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities.

Patients should be advised to report any involuntary muscle movements.

Persistent or worsening pain or burning at the injection site should be reported immediately.

Avoid prolonged exposure to the sun.

Drug Interactions

~~NARCOTICS AND BARBITURATES~~

~~The CNS depressant effects of narcotics and barbiturates are additive with promethazine hydrochloride.~~

CNS Depressants - ~~It~~ Phenergan Injection may increase, prolong, or intensify the sedative action of central-nervous-system depressants, such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. When given concomitantly with ~~promethazine hydrochloride~~ Phenergan Injection, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of ~~promethazine~~ Phenergan Injection relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

Epinephrine - Although reversal of the vasopressor effect of epinephrine has not been reported with ~~promethazine~~ Phenergan Injection, ~~the possibility should be considered~~ it is recommended that epinephrine NOT be used in the case of ~~promethazine~~ Phenergan Injection overdose.

Anticholinergics - Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

Monoamine Oxidase Inhibitors (MAOI) - Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly. Although such a reaction has not been reported with ~~promethazine~~ Phenergan Injection, the possibility should be considered.

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Laboratory Test Interactions (TEXT RELOCATED FROM ADVERSE REACTIONS)

The following laboratory tests may be affected in patients who are receiving therapy with Phenergan Injection:

Pregnancy Tests - Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test - An increase in glucose tolerance has been reported in patients receiving promethazine HCl.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term animal studies have not been performed to assess the carcinogenic potential of Phenergan Injection, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility. Phenergan Injection was nonmutagenic in the Ames *Salmonella* test system.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Teratogenic effects have not been demonstrated in rat feeding studies at doses of 6.25 and 12.5 mg/kg (approximately 2.1 and 4.2 times the maximum recommended human daily dose) of Phenergan Injection. Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats.

There are no adequate and well-controlled studies of Phenergan Injection in pregnant women. Because animal reproduction studies are not always predictive of human response, Phenergan Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adequate studies to determine the action of the drug on parturition, lactation and development of the animal neonate have not been conducted.

Nonteratogenic Effects

Phenergan Injection received within two weeks of delivery may inhibit platelet aggregation in the newborn.

Labor and Delivery

Phenergan Injection may be used alone or as an adjunct to narcotic analgesics during labor (see "DOSAGE AND ADMINISTRATION"). Limited data suggest that use of Phenergan Injection during labor and delivery does not have an appreciable effect on the duration of labor or delivery and does not increase the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown. (See also "*Nonteratogenic Effects*.")

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Nursing Mothers

It is not known whether Phenergan Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Phenergan Injection is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Phenergan Injection should be used with caution in pediatric patients 2 years of age and older (see "WARNINGS—Use in Pediatric Patients").

Use in Geriatric Patients (approximately 60 years or older) [TEXT RELOCATED FROM WARNINGS]

Since therapeutic requirements for sedative drugs tend to be less in geriatric patients, the dosage should be reduced for these patients.

ADVERSE REACTIONS

CNS Effects

Drowsiness is the most prominent CNS effect of this drug. Extrapyramidal reactions may occur with high doses; this is almost always responsive to a reduction in dosage. Other reported reactions include dizziness, lassitude, tinnitus, incoordination, fatigue, blurred vision, euphoria, diplopia, nervousness, insomnia, tremors, convulsive seizures, oculogyric crises, excitation, catatonic-like states, and hysteria, and hallucinations.

Cardiovascular Effects

Tachycardia, bradycardia, faintness, dizziness, and increases and decreases in blood pressure have been reported following the use of ~~promethazine hydrochloride~~ Phenergan Injection. Venous thrombosis at the injection site has been reported. INTRA-ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see "WARNINGS—Inadvertent Intra-arterial Injection").

Gastrointestinal Effects

Nausea and vomiting have been reported, usually in association with surgical procedures and combination drug therapy.

Allergic Reactions

These include urticaria, dermatitis, asthma, and photosensitivity. Angioneurotic edema has been reported.

Other Reported Reactions

Leukopenia and agranulocytosis, usually when Phenergan has been used in association with other known marrow-toxic agents, have been reported. Thrombocytopenic purpura and jaundice of the obstructive type have been associated with the use of ~~promethazine~~ Phenergan. The

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jaundice is usually reversible on discontinuation of the drug. Subcutaneous injection has resulted in tissue necrosis. Nasal stuffiness may occur. Dry mouth has been reported.

~~LABORATORY TESTS~~ [TEXT RELOCATED TO PRECAUTIONS]
~~The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:~~

~~Pregnancy Tests—Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.~~

~~Glucose Tolerance Test - An increase in glucose tolerance has been reported in patients receiving promethazine hydrochloride.~~

Paradoxical Reactions (Overdosage)
Hyperexcitability and abnormal movements, which have been reported in ~~children~~ pediatric patients following a single administration of ~~promethazine~~ Phenergan Injection, may be manifestations of relative overdosage, in which case, consideration should be given to the discontinuation of the ~~promethazine~~ Phenergan Injection and to the use of other drugs. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

~~Management of~~ OVERDOSAGE
Signs and symptoms of overdosage range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness.

Stimulation may be evident, especially in ~~children~~ pediatric patients and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in pediatric patients receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.

Atropine-like signs and symptoms – dry mouth, fixed, dilated pupils, flushing, etc., as well as gastrointestinal symptoms, may occur.

~~Treatment~~
~~The~~ Treatment of overdosage is essentially symptomatic and supportive. ~~Early gastric lavage may be beneficial if promethazine has been taken orally. Centrally acting emetics are of little use.~~ Only in cases of extreme overdosage or individual sensitivity do vital signs, including respiration, pulse, blood pressure, temperature, and EKG, need to be monitored. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. Note that any depressant effects of Phenergan Injection are not reversed by naloxone.

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Avoid analeptics, which may cause convulsions. ~~Severe hypotension usually responds to the administration of levarterenol or phenylephrine.~~ The treatment of choice for resulting hypotension is administration of intravenous fluids, accompanied by repositioning if indicated. In the event that vasopressors are considered for the management of severe hypotension which does not respond to intravenous fluids and repositioning, the administration of levarterenol or phenylephrine should be considered. EPINEPHRINE SHOULD NOT BE USED, since its use in a patient with partial adrenergic ~~blockage~~ blockade may further lower the blood pressure. Extrapyramidal reactions may be treated with anticholinergic antiparkinson agents, diphenhydramine, or barbiturates. ~~Additional measures include~~ Oxygen may also be administered; ~~and intravenous fluids.~~ Limited experience with dialysis indicates that it is not helpful.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Do not use Phenergan Injection if solution has developed color or contains precipitate.

To avoid the possibility of physical and/or chemical incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

Important Notes on Administration

The preferred parenteral route of administration for ~~promethazine hydrochloride~~ Phenergan Injection is by deep intramuscular injection. The proper intravenous administration of this product is well tolerated, but use of this route is not without some hazard. Not for subcutaneous administration!

INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see "WARNINGS—Inadvertent Intra-arterial Injection"). SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (see "CONTRAINDICATIONS").

Injection into or near a nerve may result in permanent tissue damage.

When used intravenously, ~~promethazine hydrochloride~~ Phenergan Injection should be given in concentration no greater than 25 mg/mL at a rate not to exceed 25 mg per minute; it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

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The TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is suitable for substances to be administered intravenously only. It is intended for use with injection sets specifically manufactured as "needle-less" injection systems. As of the date of this circular, the TUBEX BLUNT POINTE is compatible with LifeShield® Prepierced Reseal injection site, Inter-Link® Injection Site, SafeLine® Injection Site, User-Gard® Intermittent Injection Cap, and SafSite® reflux valve*.

The TUBEX® Sterile Cartridge-Needle Unit is suitable for substances to be administered intravenously or intramuscularly.

Allergic Conditions
The average adult dose is 25 mg. This dose may be repeated within two hours if necessary, but continued therapy, if indicated, should be via the oral route as soon as existing circumstances permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The average adult dose for amelioration of allergic reactions to blood or plasma is 25 mg.

Sedation
In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of ~~promethazine hydrochloride~~ Phenergan Injection.

Nausea and Vomiting
For control of nausea and vomiting, the usual adult dose is 12.5 to 25 mg, not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or intravenously and dosage of analgesics and barbiturates reduced accordingly.

Preoperative and Postoperative Use
As an adjunct to preoperative or postoperative medication, 25 to 50 mg of ~~promethazine hydrochloride~~ Phenergan Injection in adults may be combined with appropriately reduced doses of analgesics and atropine-like drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

Obstetrics
Phenergan Injection in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25 to 75 mg (average dose, 50 mg) ~~promethazine hydrochloride~~ Phenergan Injection may be given intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. ~~Amnesic agents may be administered as necessary~~: If necessary, Phenergan Injection with a reduced dose of analgesic may be repeated once or twice at four-hour intervals in the course of a normal labor. A maximum total dose of 100 mg of Phenergan Injection may be administered during a 24-hour period to patients in labor.

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~~CHILDREN~~ **Pediatric Patients**
Phenergan Injection is not recommended for use in pediatric patients less than two years of age.

In ~~children under the age of 12 years~~ pediatric patients 2 years of age and older, the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication, the suggested dose is 0.5 mg per lb. of body weight in combination with an equal dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in children pediatric patients (see "WARNINGS—Use in **Pediatric Patients**").

HOW SUPPLIED
Phenergan® (promethazine HCl) Injection is available in the following dosage strengths in **TUBEX® BLUNT POINTE™** Sterile Cartridge Units and Sterile Cartridge-Needle Units, packaged in boxes of 10 **TUBEX®** as follows:

25 mg per mL, NDC 0008-0416-50, 1 mL size **BLUNT POINTE™**.
25 mg per mL, NDC 0008-0416-01, 1 mL size (22 gauge x 1-1/4 inch needle).
50 mg per mL, NDC 0008-0417-01, 1 mL size (22 gauge x 1-1/4 inch needle).

TUBEX® BLUNT POINTE™ Sterile Cartridge Units and Sterile Cartride-Needle Units are intended for use with the **TUBEX®** Injector, which is a reusable plastic injector designed for administration of these products.

Store at room temperature, between 15°C-25°C (59°F-77°F).
Protect from light. ~~Use carton to protect contents from light.~~ Keep covered in carton until time of use.
Do not use if solution ~~is discolored~~ has developed color or contains a precipitate.

Also Available:
Phenergan Injection is also available in 1-mL ampuls ~~of 1 mL~~, in packages of 25 ampuls, as follows:

25 mg per mL, NDC 0008-0063-01.
50 mg per mL, NDC 0008-0746-01.

* * *

LETTER FROM FDA TO WYETH DATED SEPTEMBER 18, 1998 (DEFENDANT'S TRIAL EXHIBIT H)

[logo]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Stamp: SEP 18 1998

Stamp: RECEIVED
SEP 25 1998
JOHN SENECA, R. PH.

Stamp: RECEIVED
SEP 25 1998
Nanette E. Holston
U.S. Regulatory Affairs

NDA 8-857/S-009

Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

Attention: Nanette E. Holston
Manager
U.S. Regulatory Affairs

Dear Ms. Holston:

Please refer to your supplemental new drug application dated September 21, 1981, received September 21,

1981, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenergan (promethazine hydrochloride) Injection, 25 and 50 mg/mL.

We acknowledge receipt of your submissions dated May 3, 1988, February 1, March 1, and May 15, 1989, January 7, 1992, August 6, 1996, and May 8 and August 21, 1998. Your submission of May 8, 1998, constituted a full response to our February 21, 1997, action letter.

This supplemental new drug application provides for revised labeling.

We have completed the review of this supplemental application, including the draft package insert dated May 8, 1998, and the final printed carton and container labels dated August 21, 1998, and it is approved effective on the date of this letter.

The final printed labeling (FPL) for the package insert must be identical to the draft package insert submitted May 8, 1998.

Please submit 20 copies of the FPL for the package insert as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement 8-857/S-009." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of the labeling may be required.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

4

If you have any questions, contact Mr. David Hilfiker, Project Manager, at (301) 827-1046.

Sincerely yours,

/s/

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: RRA, KFB, VDV, NEH, [illegible], CL, JL, DCM, JPS, JRV, GRO, RA Log

FACSIMILE FROM WYETH TO FDA DATED OCTOBER 23, 1998 (PLAINTIFF'S SUMMARY JUDGMENT EXHIBIT 13)

[handwritten: NDA #8-857]

Wyeth-Ayerst Drug Regulatory Affairs

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DATE:	October 23, 1998
TO:	Mr. David Hilfiker Project Manager Division of Pulmonary Drug Products Food and Drug Administration
FAX:	301-827-1271
FROM:	John Seneca
TELEPHONE:	(610) 902-3724
FACSIMILE:	(610) 964-5972
DEPARTMENT:	U.S. Regulatory Affairs
ADDRESS:	Wyeth-Ayerst St. Davids Center: 170 Radnor-Chester Road, St. Davids PA 19087

NO. OF PAGES (including cover sheet): 1

Dear Mr. Hilfiker:

Reference is made to our approved New Drug Application No. 8-857 for Phenergan® (promethazine) Injection, and to supplement 009, approved on September 18, 1998, which provides for revised labeling.

In preparing the Final Printed Labeling (FPL) for S-009, we have identified a small textual revision that we believe is appropriate for the "Dosage and Administration" section. The revision concerns the third sentence in the "Pediatric Patients" subsection, which currently reads "As an adjunct to premedication, the suggested does is 0.5 mg per lb. of body weight in combination with an equal does of narcotic or barbiturate and the appropriate does of an atropine-like drug." For consistency with the information for adults in the "Preoperative and Postoperative Use" subsection of "Dosage and Administration" and the "Indications" section, which indicate the need for reduced doses of concomitant premedication analgesics, we wish to change the sentence to "As an adjunct to premedication, the suggested dose is 0.5 mg per lb. of body weight in combination with an *appropriately reduced* dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug" (change shown in italics).

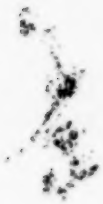
We hope this change will meet with approval for incorporation into the FPL. Please contact me if you have any questions.

Wyeth-Ayerst Laboratories

/s/

John Seneca
Coordinator, U.S. Regulatory Affairs

PHOTOGRAPHS (PAINTIFF'S TRIAL EXHIBITS 37, 39, 40, 41)



PHENERGAN LABELING IN EFFECT IN 2000
(DEFENDANT'S SUMMARY JUDGMENT
EXHIBIT A)

Phenergan®
(promethazine HCl)
Injection
CI 3727-7

Phenergan®

(promethazine HCl)

Injection

DESCRIPTION

Phenergan (promethazine HCl) Injection is a sterile, pyrogen-free solution for deep administration or slow venous administration. Promethazine HCl (10H-phenothiazine-10-ethanamine, N,N,α-trimethyl-monohydrochloride, (±)) is a racemic compound and has the following structural formula:

C17H20N2S • HCl MW=320.89

Each mL of the TUBEX® and RUBY® BLUNT POINTE™ Sterile Cartridge Units contains either 25 or 50 mg promethazine HCl with 0.1 mg edetate disodium, 0.64 mg calcium chloride, not more than 5 mg monothioglycerol, and 5 mg phenol in Water for Injection. The pH range is 4.0 to 5.5. Buffered with sodium potassium acetate and is sealed under nitrogen.

Phenergan (promethazine HCl) Injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

CLINICAL PHARMACOLOGY

Promethazine HCl is a phenothiazine derivative which possesses antihistaminic, sedative, antiemetic, antimotion sickness, antispasmodic, and anticholinergic effects. Promethazine is a competitive H1 receptor antagonist, but does not block the release of histamine. Structural differences from the neuroleptic phenothiazines result in no neuroleptic (CNS) or hypotensive antagonistic properties. In therapeutic doses, promethazine HCl produces no significant effects on the cardiovascular system. Clinical effects are generally observed within 5 minutes of an intramuscular injection and within 20 minutes of an intravenous injection. Duration of action is four to six hours, although effects may persist up to 12 hours. Promethazine HCl is metabolized in the liver, with the formation of promethazine sulfoxide, N-demethylpromethazine being the predominant metabolite appearing in the urine. Following intravenous administration in healthy volunteers, the plasma half-life for promethazine has been reported to range from 9 to 16 hours. The major plasma half-life for promethazine after intramuscular administration in healthy volunteers has been reported to be 8.8 ± 3.4 hours.

INDICATIONS AND USAGE

Phenergan Injection is indicated for the following conditions:

1. Administration of allergic reactions in blood or plasma.
2. In anaphylaxis, as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
4. For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
5. Active treatment of motion sickness.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
8. Preoperative, postoperative and obstetric (during labor) sedation.
9. Symptomatic relief of upper respiratory infections, such as nonspecific bronchoconstrictor conditions/ear surgery, and motion sickness, with reduced amounts of respirations or other narcotic analgesics as an adjunct to anesthesia and analgesia.

CONTRAINDICATIONS

Phenergan Injection is contraindicated in comatose states and in persons who have demonstrated an idiosyncrasy or hypersensitivity to promethazine or other phenothiazines.

Under no circumstances should Phenergan Injection be given by intra-arterial injection due to the likelihood of severe complications and the possibility of resultant gangrene (see "WARNINGS—Intra-arterial injection").

Phenergan Injection should not be given by the subcutaneous route; evidence of chemical irritation has been noted, and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular infusion.

WARNINGS

CNS Depression

Phenergan Injection may impair the mental and physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. (see "PRECAUTIONS—Information for Patients").

Lower Seizure Threshold

Phenergan Injection may lower seizure threshold and should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

Bone-Marrow Depression

Phenergan Injection should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known myelotoxic agents.

Use in Pediatric Patients

PHENERGAN INJECTION IS NOT RECOMMENDED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN INJECTION TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO PREDUCED VOMITING OF UNKNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN INJECTION ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN INJECTION SHOULD BE AVOIDED IN PEDIATRIC PATIENTS WHERE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASES.

Postoperative large dosages of antihistaminics, including Phenergan Injection, in pediatric patients may cause hallucinations, convulsions, and sudden death. In pediatric patients who are suspected of developing early dehydration, there is an increased susceptibility to dystonias even with the use of Phenergan Injection.

Sulfite-Sensitive Patients

Due to the latent presence of sulfites and ureas in the urine most commonly used for intravenous infusion, extreme care should be exercised to avoid perivascular administration or inadvertent intra-arterial injection. Agents compatible with epinephrine are preferred injection of Phenergan Injection, alone or in conjunction with other drugs intended for intravenous use, suggest that pure, sensitive chemical-sensitive sensory system of blood vessels, and resultant gangrene requiring amputation are likely under such circumstances. Extravascular injection may be minimized if all the above reported side particulars for administration of arterial absorption of the needle is now assessed. There is no proven treatment of management of this condition after it occurs, although sympathetic block and hyperoxygenation are commonly employed during the acute management because of the rapidity of arterial spasm/vessels with other known pharmacological antagonists. Injection of such blood does not preclude vaso-arterial vessels above insult, because blood is destroyed upon contact with Phenergan Injection. Use of cartilage with rigid dilatation or of small bore needles might otherwise have a potential beneficial if this is to not upon done.

When used intravenously Phenergan Injection should be given at a concentration no greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any potent drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended intravenous injection of Phenergan Injection, the injection should be stopped immediately to permit re-evaluation of possible extravascular placement or perivascular extravasation.

Visual Inspection

This product is light sensitive and should be inspected before use and discarded if either color or particulate is observed.

Other Considerations

Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea.

Administration of promethazine has been associated with reported cholestatic jaundice.

PRECAUTIONS

General

Drugs having anticholinergic properties should be used with caution in patients with narrow angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction and bladder neck obstruction.

Phenergan Injection should be used cautiously in patients with cardiovascular disease or impairment of liver function.

Information for Patients

Phenergan Injection may cause marked drowsiness or impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. with Phenergan Injection may enhance impairment. Patients' activities should be supervised to avoid potential harm in after-taking or in other hazardous activities.

Patients should be advised to report any involuntary muscle movements.

Persistent or worsening pain or burning at the injection site should be reported immediately.

Avoid prolonged exposure to the sun.

Drug Interactions

CNS Depressants - Phenergan Injection may increase, prolong, or intensify the sedative action of central-nervous-system depressants, such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. when given concomitantly with Phenergan Injection. The dose of the following should be reduced by at least one half, and the dose of barbiturates should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of Phenergan Injection initiates by a syncope, may lead to unconsciousness and motor hyperactivity as the patient can pass. Close symptomatic study discussions with addiction control of the pain.

Epinephrine - Although reversal of the vasoconstrictor effect of epinephrine has not been reported with Phenergan Injection, it is recommended that epinephrine NOT be used in the case of Phenergan injection overdose.

Anticholinergics - Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

Monoamine Oxidase Inhibitors (MAOI) - Drug interactions, including an increased incidence of side pharmacological effects, have been reported when some MAOI and phenothiazines are used concomitantly. Although such a reaction has not been reported with Phenergan Injection, the possibility should be considered.

Laboratory Test Interactions

The following laboratory tests may be affected in patients who are receiving therapy with Phenergan Injection:

Pregnancy Tests - Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test - An increase in glucose tolerance has been reported in patients receiving promethazine HCl.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to assess the carcinogenic potential of Phenergan Injection, nor are there other animal or human data concerning carcinogenesis, mutagenicity, or impairment of fertility. Phenergan Injection was nonmutagenic in the Ames Salmonella test system.

Pregnancy

Teratogenic Effects—Pregnancy Category C

Teratogenic effects have not been demonstrated in rat feeding studies at doses of 6.25 and 12.5 mg/kg (approximately 2.1 and 4.2 times the maximum recommended human dose, based on Phenergan injection). Fetal doses of 25 mg/kg are spontaneously have been found to produce fetal mortality in rats.

There are no adequate and well-controlled studies of Phenergan Injection in pregnant women. Because animal reproduction studies are not always predictive of human response, Phenergan Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adequate studies to determine the effect of the drug on perinatal, fetal and development of the prenatal materials have not been conducted.

Nonteratogenic Effects

Phenergan Injection has been reported to have the ability of patients may inhibit platelet aggregation in the newborn.

Labor and Delivery

Phenergan Injection may be used alone or as an adjunct to narcotic analgesics during labor (see "DOSAGE AND ADMINISTRATION"). Limited data suggest that use of Phenergan Injection during labor and delivery does not have an appreciable effect on the duration of labor or delivery and does not contribute the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown. (See also "Nonteratogenic Effects.")

Nursing Mothers

It is not known whether Phenergan Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Phenergan Injection is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Phenergan Injection should be used with caution in pediatric patients 2 years of age and older (see "WARNINGS—Use in Pediatric Patients").

Use in Geriatric Patients (approximately 65 years or older)

Since the geriatric responsiveness for sedative drugs tend to be less or greater in patients, the dosage should be reduced for these patients.

ADVERSE REACTIONS

CNS Effects

Drowsiness is the most prominent CNS effect of this drug. Extrapyramidal reactions may occur with high doses. This is dose-related and responsive to a reduction in dosage. Other reported reactions are dizziness, disorientation, confusion, excitation, fatigue, blurred vision, diplopia, tinnitus, vertigo, headache, insomnia, tremors, convulsive seizures, neuroleptic malignant syndrome, hallucinations (daytime and dream), nightmare and hyperreflexia.

Cardiovascular Effects

Tachycardia, bradycardia, faintness, dizziness, and decreases or increases in blood pressure have been reported following the use of Phenergan Injection. Postural hypotension, as the case can also be

PLEASE NOTE: THE WYETH AYERST METAL TUBE/3 HYPODERMIC SYRINGE AND TUBE/3 FAST TRAK SYRINGE HAVE BEEN DISCONTINUED AND REPLACED BY THE TUBEX INJECTOR. EXCHANGE OF THESE DISCONTINUED SYRINGES IS AVAILABLE, FREE OF CHARGE, FROM YOUR WYETH-AYERST SALES REPRESENTATIVE, OR FROM WYETH AYERST DIRECTLY FOR LOADING #1ML (tan) DIATHAL. #INFORMATION ON THESE DISCONTINUED SYRINGES, CONTACT THE MEDICAL AFFAIRS DEPARTMENT AT WYETH AYERST LABORATORIES, P.O. BOX 8299, PHILADELPHIA, PA 19101

TUBEX® Injector

NOTE: The TUBEX Injector is #REUSABLE. do not discard.

TUBEX Sterile Cartridge Needle Unit
DIRECTIONS FOR USE:

TUBEX® BLUNT POINTE™ Sterile Cartridge Unit
DIRECTIONS FOR USE.

TUBEX BLUNT POINTE Sterile Cartridge Unit is intended for use with injection units specifically manufactured as "needle-less" injection systems. As of the date of this circular TUBEX BLUNT POINTE Sterile Cartridge Unit is compatible with LectaShot® Preparated Reveal injection site, SmartJet® Injection Site, Solo-Cart® Injection Site, Uno-Cart® interventus injection Cap, and SoftJet® reflex valve.

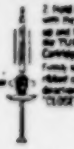
Consult manufacturer's recommendations regarding "Directions for Use" of the "needle less" injection system.

#FOR THE ASEPTIC TECHNIQUE FOR ALL MANIPULATIONS OF STERILE PARTS.

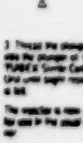
To load a TUBEX Sterile Cartridge Unit into the TUBEX injector

1. Turn the ribbed collar to the "OPEN" position until it stops.

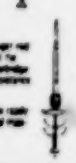
TUBEX Sterile Cartridge Needle Unit



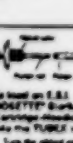
TUBEX BLUNT POINTE Sterile Cartridge Unit



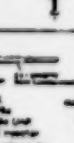
2. Hold the injector with the clear grip end fully down and TUBE/3 Sterile Cartridge Unit firmly against the ribbed collar in the direction of the "CLOSE" arrow.



3. Thread the plunger rod onto the plunger of the TUBEX Sterile Cartridge Unit until slight resistance is felt.

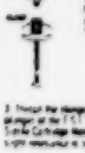


The injection is now ready for use in the usual manner.

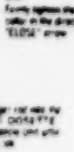


To load an E.S.I. DOSETTE® Sterile Cartridge-Needle Unit into the TUBEX injector

1. Turn the ribbed collar to the "OPEN" position until it stops.

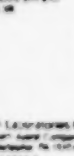


2. Hold the injector with the clear grip end fully down and E.S.I. DOSETTE Sterile Cartridge Needle Unit firmly against the ribbed collar in the direction of the "CLOSE" arrow.



3. Thread the plunger rod onto the plunger of the E.S.I. DOSETTE Sterile Cartridge Needle Unit until slight resistance is felt.

The injection is now ready for use in the usual manner.



4. Engage the needle cap assembly by pulling the cap down over the sterile cartridge hub. The needle is fully engaged when the outer hub is completely covered.

The injection is now ready for use in the usual manner.

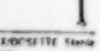
To administer TUBE 3/DOSETTE Sterile Cartridge Needle Units:

Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely in one hand and pull. Immediately engage needle cover with other hand. ADVICE by barring both rigidly on the plunger and inject.

To administer TUBEX BLUNT POINTE Sterile Cartridge Units:

"Needle less" IV

For administration of a syringe to patient or infusion set with Luer adapter (female)



Remove rubber cover by grasping it securely in one hand and pull. The SoftJet® (tan) sheet over needle. Hold the Luer slip fitting of the TUBEX BLUNT POINTE sterile cartridge to patient line with a gentle, individually engaged twisting motion. Immediately engage needle cover with other hand. Immediately wipe the Luer slip fitting of the TUBEX BLUNT POINTE sterile cartridge to patient line with a gentle, individually engaged twisting motion. Immediately engage needle cover with other hand. ADVICE by barring both rigidly on the plunger and inject.

To administer TUBEX BLUNT POINTE Sterile Cartridge Units